Multidrug-resistant Gram-negative bacterial infections

Nenad Macesic, Anne-Catrin Uhlemann, Anton Y Peleg

Multidrug-resistant Gram-negative bacterial infections cause significant morbidity and mortality globally. These pathogens easily acquire antimicrobial resistance (AMR), further highlighting their clinical significance. Third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales (eg, *Escherichia coli* and *Klebsiella* spp), multidrug-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii* are the most problematic and have been identified as priority pathogens. In response, several new diagnostic technologies aimed at rapidly detecting AMR have been developed, including biochemical, molecular, genomic, and proteomic techniques. The last decade has also seen the licensing of multiple antibiotics that have changed the treatment landscape for these challenging infections.

Lancet 2025; 405: 257–72

Department of Infectious Diseases, The Alfred Hospital and School of Translational Medicine (N Macesic MBBS, Prof A Y Peleg MBBS), **Centre to Impact AMR** (N Macesic, Prof A Y Peleg), **and Infection Program, Monash Biomedicine Discovery Institute** (Prof A Y Peleg), **Monash University, Melbourne, VIC, Australia; Department of Medicine, Division of Infectious Diseases, Columbia University Irving Medical Center, New York, NY, USA** (A-C Uhlemann MD)

Correspondence to:
Prof Anton Y Peleg, Department of Infectious Diseases, The Alfred Hospital and School of Translational Medicine, Monash University, Melbourne, VIC 3004, Australia
anton.peleg@monash.edu

Introduction

Antimicrobial resistance (AMR) is one of the most crucial public health challenges of the 21st century. In 2021, an estimated 4·71 million deaths were associated with bacterial AMR, with low-income and middle-income countries disproportionately affected.[1,2] Multidrug-resistant Gram-negative bacteria (MDR-GNB) are responsible for much of this threat. In recent decades, these pathogens have become a leading cause of both community and health-care-associated infections,[3] and until recently, the pipeline of new therapeutics for MDR-GNB was almost non-existent. Multiple factors have contributed to the expansion of MDR-GNB resistance, including the misuse and overuse of antibiotics in both human and animal health, the absence of clean water and sanitation, increasing complexity of medical care, and inadequate infection prevention and control.[4,5] On a biological level, these bacteria are incredibly adept at spreading AMR by transfer of mobile genetic elements such as plasmids, for example.[5] Unfortunately, AMR has continued to worsen, with resistance to antibiotics of last resort, such as carbapenems, polymyxins, and even novel β-lactam and β-lactamase inhibitor combinations now being reported,[6–8] which makes the prospect of pan-drug resistance in Gram-negative bacteria increasingly a reality.[9]

The clinical syndromes caused by MDR-GNB infections are the same as those caused by antibiotic-susceptible Gram-negative bacteria. These syndromes include cystitis, complicated urinary tract infection (UTI; eg, pyelonephritis), hospital-acquired or ventilator-associated pneumonia, and intra-abdominal and bloodstream infections.[5,10,11] Risk factors for MDR-GNB infections are consistent across different categories of MDR-GNB and include the presence of comorbidities, previous antibiotic use, previous colonisation with MDR-GNB, previous intensive care unit stay, mechanical ventilation, dialysis, length of hospital stay, and travelling to regions with a high prevalence of MDR-GNB.[12–15] Due to a crucial unmet need, diagnostics have advanced to include the use of multiplex PCR assays, mass spectrometry techniques, and bacterial whole genome sequencing. Similarly, new therapeutics for MDR-GNB have progressed along the development pipeline in the last 5 years and include novel β-lactam and β-lactamase inhibitor combinations, tetracyclines, aminoglycosides, and novel siderophore-like cephalosporins (eg, cefiderocol).[16] In addition to antibiotic agents, there has also been a push for new treatment approaches such as phage therapy and anti-virulence approaches.[17,18]

Clinically important mechanisms of AMR

Antibiotics have been developed to target multiple sites of the bacterial cell to impair bacterial growth or cause cell death (figure 1). Gram-negative bacteria are highly capable of developing resistance to antibiotics via a range of mechanisms, including antibiotic modification or degradation (eg, β-lactamase hydrolysis of β-lactam antibiotics), decreasing antibiotic entry into the bacterial cell (eg, loss of porins), altering the target site of the antibiotic (eg, ribosomal alteration), and increasing antibiotic efflux from the bacterial cell (eg, with overexpression of transmembrane efflux pumps; table 1).[19,20,29,33] These mechanisms can arise from mutations in the bacterial chromosome, or from acquisition of new resistance determinants, particularly via plasmids. These mobile genetic elements often carry genes coding for resistance to multiple antibiotic classes.

Definitions of AMR

With this rich repertoire of mechanisms and modes of spread, resistance to multiple classes of antibiotics in Gram-negative bacteria has become a prominent public health problem. In 2012, a standardised international terminology for AMR was developed[34] in which multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antibiotic categories, extensive drug resistance was defined as non-susceptibility to at least one agent in all but one or two antibiotic categories, and pan-drug resistance was defined as non-susceptibility to all agents in all antibiotic categories. More recently, a clinical definition of difficult-to-treat resistance (DTR) for Gram-negative bacteria was developed, defined as treatment-limiting resistance to all first-line agents; that is, all β-lactams, including carbapenems and β-lactamase inhibitor combinations (not including novel combinations), and fluoroquinolones.[35] This definition distinguishes low

SHOUT
SHARE
IT

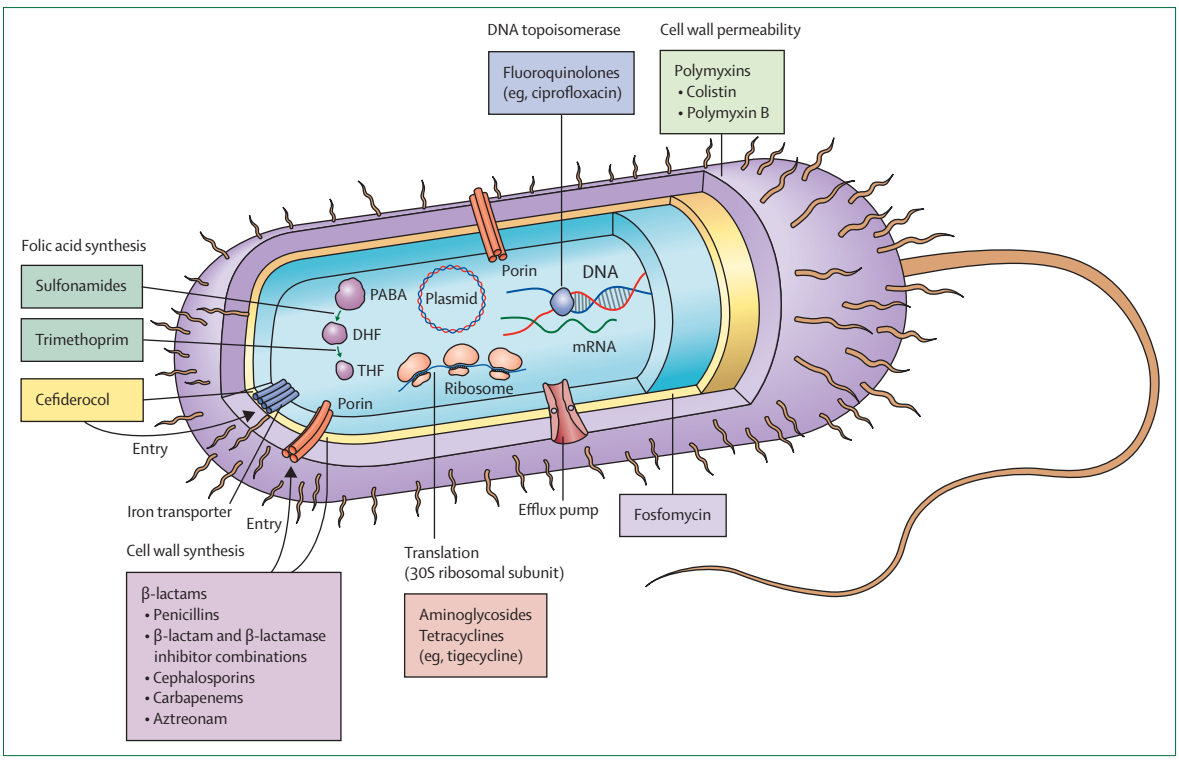


Figure 1: **Mechanisms of action of key antibiotics for the treatment of multidrug-resistant Gram-negative bacterial infections**
Several classes of antibiotics are available for the treatment of multidrug-resistant Gram-negative bacterial infections. Their mechanisms of action focus on key aspects of bacterial cell function, such as inhibiting cell wall synthesis (ie, β-lactams and fosfomycin) and function (ie, polymyxins), protein synthesis (ie, aminoglycosides and tetracyclines), folic acid synthesis (ie, trimethoprim and sulphonamides), and DNA replication (ie, fluoroquinolones). Because of increasing antimicrobial resistance, novel antibiotics have been developed to overcome some of these mechanisms; for example, by inhibiting antibiotic modification (ie, β-lactamase inhibitors) or by altering entry pathways (ie, cefiderocol, which enters via iron transporters). This figure was created with BioRender.com. DHF=dihydrofolic acid. PABA=para-aminobenzoic acid. THF=tetrahydrofolate.

toxicity first-line agents from agents with higher toxicity and less efficacy, such as aminoglycosides, polymyxins (nephrotoxicity and poor penetration in abdominal and pulmonary sites), and tigecycline (low serum levels and poor lung penetration).[31,36–38]

Clinically relevant multidrug-resistant Gram-negative pathogens

Enterobacterales

Enterobacterales include some of the most common Gram-negative pathogens. These include *Escherichia coli*, *Klebsiella* spp, and *Proteus* spp, which are common commensals of the gastrointestinal tract and often cause urinary tract, intra-abdominal, and bloodstream infections, and *Enterobacter* spp and *Serratia marcescens*, which are more commonly seen within health-care settings. The most clinically relevant resistance mechanisms of Enterobacterales include extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases, which confer resistance to narrow-spectrum penicillins (eg, benzylpenicillin and amoxycillin) and third-generation cephalosporins (eg, ceftriaxone and ceftazidime), and carbapenemases, which confer resistance to carbapenems (eg, meropenem, imipenem, and ertapenem).[10,11,39] Given the importance of these antibiotics for the treatment of Enterobacterales infections and increasing reports of resistance, WHO has declared third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales (CRE) as critical priority pathogens for novel drug development.[3]

ESBLs are a heterogeneous group of enzymes that hydrolyse the β-lactam ring in antibiotics and have a serine in the active site.[40] ESBLs are often located on mobile genetic elements such as plasmids, leading to their rapid horizontal transmission between bacterial pathogens.[19] While conferring resistance to third-generation cephalosporins, bacteria carrying these enzymes remain susceptible to carbapenems. The earliest identified ESBLs were TEM and SHV β-lactamases, with subsequent extensive spread of the CTX-M family of enzymes, particularly plasmid-borne CTX-M-15 associated with the *E coli* sequence type 131 clone.[19,41] ESBLs in Enterobacterales have now become endemic globally in both hospital and community settings, with rates of 5–25% in western Europe, more than 50% in southern and eastern Europe, 30% in Latin America, 11–13% in the USA, 30–80% in Asia (depending on country), and 10–15% for Australia and New Zealand.[40,42–44]

AmpC β-lactamases are most often found in *Enterobacter* spp, *S marcescens*, *Citrobacter freundii*, *Morganella morganii*, and *Providencia* spp. Despite their resistance to third-generation cephalosporins, these pathogens often remain susceptible to cefepime and carbapenems. AmpC can be distinguished from ESBLs by their resistance to some β-lactamase inhibitors (eg, clavulanic acid) and cephamycins (eg, cefoxitin), to which ESBLs remain susceptible.[45] *ampC* genes are most often located on the bacterial chromosome and their expression can be induced by exposure to various β-lactam antibiotics, including third-generation cephalosporins.[46] The bacteria can initially show in vitro susceptibility to these agents, but then develop resistance if induction ensues.[47] Considerable inducible chromosomal *ampC* expression is most often encountered in the *Enterobacter cloacae* complex, *Klebsiella aerogenes*, and *C freundii*, whereas *S marcescens*, *M morganii*, and *Providencia* spp. have lower levels of inducible *ampC* expression and are therefore less likely to develop third-generation cephalosporin resistance.[48–50] In contrast, plasmid-mediated *ampC* genes are typically detected in *K pneumoniae*, *E coli*, and *Salmonella* spp. and confer resistance without requiring induction.[46]

Carbapenemases are enzymes that hydrolyse a broad range of β-lactams, including carbapenems. They can be further classified as carbapenemases that rely on a serine residue in the active site (eg, KPC [Klebsiella pneumoniae carbapenemase], IMI [Imipenem-hydrolysing β-lactamase], and OXA-48 groups) or those that rely on zinc, also known as metallo-β-lactamases (eg, NDM [New Delhi metallo-β-lactamase], VIM [Verona Integron-encoded metallo-β-lactamase], and Imipenemase [IMP]).[19] With the advent of new β-lactamase inhibitors that are enzyme-specific, it has become more important to know the mechanism of carbapenem resistance to help guide optimised antibiotic choice. Carbapenem resistance in Enterobacterales can also result from non-carbapenemase mechanisms, such as ESBL overproduction, porin mutation and loss, and upregulation of efflux pumps.[8] Globally, rates of carbapenem resistance in Enterobacterales remain less than 10%, but there is substantial variation between regions, with more than 50% of *K pneumoniae* isolates from Greece and Russia being carbapenem resistant.[8,43,51,52] Rates of resistance also differ according to bacterial species, with more carbapenem resistance in *K pneumoniae*, and a higher proportion being carbapenemase producers.[53] The predominant type of carbapenemase also varies between regions, with KPCs most commonly noted in North America, Asia, and Southern Europe, while NDMs predominate on the Indian subcontinent, the Middle East, and the Balkans, and IMPs in Asia and Australia.[54,55] However, systematic sampling in community and hospital settings is not typically undertaken globally and therefore reported rates could be affected by sampling bias.

	Categories	Examples
β-lactams[19,20] (eg, piperacillin–tazobactam, cefepime, meropenem, and ceftazidime–avibactam)		
Antibiotic modification	β-lactamase enzymes	Extended-spectrum β-lactamases (SHV, TEM, and CTX-M); carbapenemases (KPC, OXA-48, NDM, IMP, and VIM)
Decreased entry	Porin mutations	*Escherichia coli* (OmpC and OmpF); *Klebsiella pneumoniae* (OmpK35 and OmpK36); *Pseudomonas aeruginosa* (OprD); *Acinetobacter baumannii* (CarO)
Increased efflux	Efflux pumps	*E coli* (AcrAB-TolC); *P aeruginosa* (MexAB-OprM); *A baumannii* (AdeABC and AdeIJK)
Aminoglycosides[21–24] (eg, gentamicin, tobramycin, and amikacin)		
Antibiotic modification	Aminoglycoside-modifying enzymes (AMEs)	N-acetyltransferases (AAC); O-adenyltransferases (ANT); O-phosphotransferases (APH)
Decreased entry	Alterations in bacterial cell outer membrane	PhoPQ; PmrAB; ParRS; CprRS
Target alteration	16S-ribosomal RNA methyltransferases (RMTs)	ArmA; RmtA; RmtB; RmtC; RmtD; RmtE; RmtF; RmtG; NpmA; NpmB; NpmC
Target alteration	30S ribosome subunit binding site mutations	*rrs* and *rpsL* gene mutations
Tetracycline derivatives[25–28] (eg, minocycline, tigecycline, and eravacycine)		
Antibiotic modification	Increased breakdown	Tet(X); Tet(X2); Tet(X3); Tet(X4)
Increased efflux	Major facilitator superfamily (MFS) of transporters	Tet(A); Tet(B); Tet(C); Tet(D)
Increased efflux	Resistance nodulation division (RND)-type multidrug efflux pumps	AdeABC; TmexCD1-ToprJ1
Target alteration	Ribosomal protein alteration	RpsJ
Fluoroquinolones[29,30] (eg, ciprofloxacin)		
Antibiotic modification	Increased breakdown	AME: AAC(6′)-Ib-cr
Increased efflux	Efflux pumps	QepA; OqxAB
Target alteration	Topoisomerase substitution	GyrA; GyrB; ParC; ParE
Target alteration	DNA gyrase protection	QnrA
Polymyxins[31] (eg, colistin and polymyxin B)		
Target alteration	Two component systems	*K pneumoniae* (PhoPQ, PmrAB, MgrB, and CrrAB); *P aeruginosa* (PhoPQ, PmrAB, ParRS, ColRS, and CprRS); *A baumannii* (PmrAB)
Target alteration	Mobile (plasmid-mediated) colistin resistance enzymes	Encoded by *mcr* genes
Fosfomycin[32]		
Antibiotic modification	Fosfomycin modifying enzymes	Encoded by *fos* genes
Decreased entry	Alterations in fosfomycin transporters	GlpT; UhpT; CyaA; PtsI

Table 1: **Mechanisms of resistance to key classes of antibiotics used for the treatment of multidrug-resistant Gram-negative bacterial infections**

Pseudomonas aeruginosa

P aeruginosa is a common nosocomial pathogen that can readily develop resistance to multiple antibiotics. While resistance in Enterobacterales is driven by acquired β-lactamases, resistance in *P aeruginosa* is often due to the presence of efflux pumps that actively remove multiple antibiotics (eg, MexAB-OprM), and mutations of porins (eg, OprD) that decrease permeability to

antibiotics.[56] These factors act in concert with overexpression of *Pseudomonas*-derived cephalosporinase (PDC), a chromosomal AmpC-type β-lactamase. In addition to these intrinsic mechanisms, *P aeruginosa* can also acquire resistance mechanisms via plasmids, such as β-lactamase genes (including carbapenemase genes—eg, bla_{VIM} and bla_{KPC}) and quinolone resistance.[57,58] Global rates of carbapenem resistance in *P aeruginosa* generally range from 10–20% and MDR rates from 5–30%, depending on the region and the site of infection.[8,43,57,59,60] Due to the novelty of the DTR definition, few epidemiological data are available that document DTR prevalence in *P aeruginosa* globally, with 2·3% and 16·9% representing the proportion of *P aeruginosa* that have DTR reported in the multicentre US study of Gram-negative bacteria bloodstream isolates that proposed the definition of DTR and in the global ATLAS surveillance network, respectively.[35,61]

Acinetobacter baumannii

Similar to *P aeruginosa*, AMR in *Acinetobacter baumannii* results from multiple coexisting mechanisms including porin mutations and the production of multiple β-lactamases, aminoglycoside-modifying enzymes, and efflux pumps.[62,63] While these mechanisms often act together, the most concerning development leading to the rise of carbapenem resistance has been the acquisition of carbapenemases, predominately the OXA-type (eg, OXA-23) and metallo-β-lactamases (eg, IMP, NDM, and VIM).[62] In a recent global survey, 91% of carbapenem resistant isolates carried a carbapenemase gene, with bla_{OXA-23} accounting for 88%.[64] It is possible for multiple carbapenemases to be acquired by the same bacterium, both in *A baumannii* and other Gram-negative pathogens. Rates of carbapenem resistance in *A baumannii* are greater than 30% globally, with many regions, such as southern and eastern Europe reaching greater than 50%, and parts of Asia greater than 80%.[8,43,65,66]

Recent advances in diagnostics

Rapid diagnosis of AMR helps guide treatment and has been shown to improve timeliness and appropriateness of antibiotic use, and in some cases, patient outcomes.[67–71] Traditional laboratory techniques for antibiotic susceptibility testing require culture of an organism with subsequent quantitative (eg, broth dilution tests or antibiotic gradient methods) or qualitative (eg, disk diffusion) phenotypic methods for detecting resistance.[72] Despite some of these techniques being automated in commercial instruments,[73] turn-around times for susceptibility testing results can vary from 18 h to 48 h

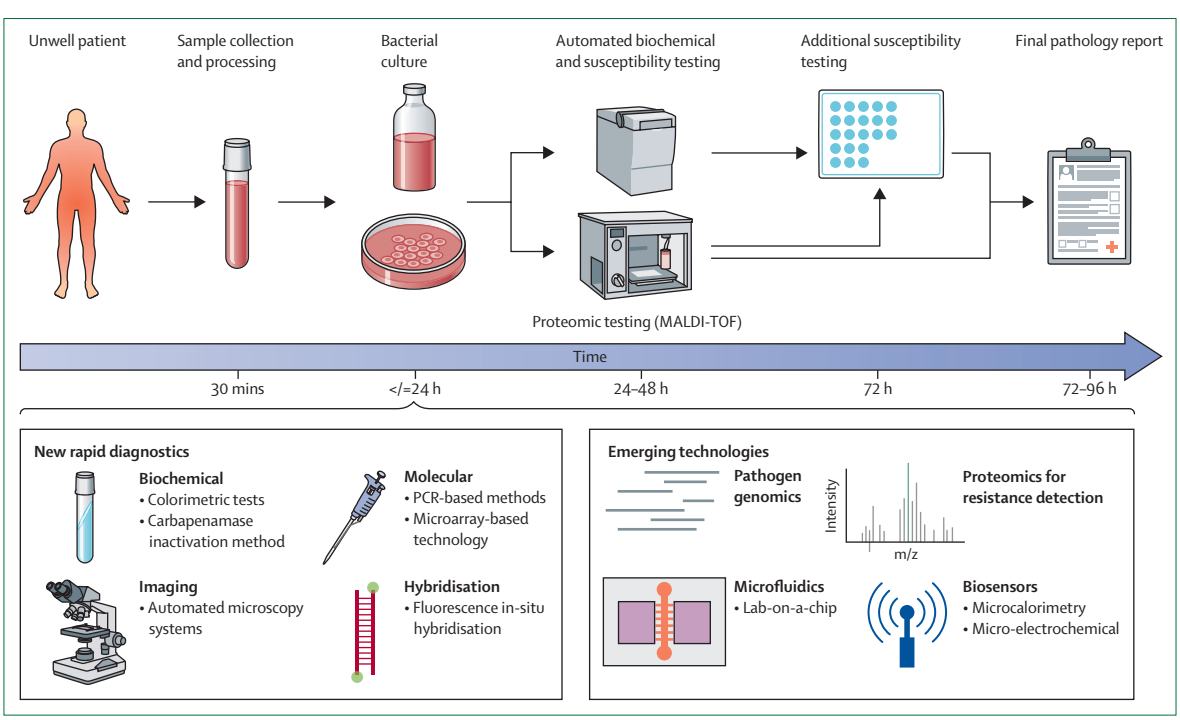


Figure 2: **Diagnostic testing of multidrug-resistant Gram-negative bacteria**

Diagnosis of multidrug-resistant Gram-negative bacterial infections involves both species identification and antibiotic susceptibility testing. Although clinical microbiology laboratories have undergone automation of these processes and have seen the introduction of proteomic methods, such as MALDI-TOF, delays in turnaround time remain and might affect patient outcomes. New biochemical, molecular (eg, PCR), automated microscopy, and hybridisation-based rapid diagnostics now allow faster detection of antimicrobial resistance, including by testing clinical samples directly. Emerging technologies are seeking to improve both the speed of testing and provide more detailed information regarding the underlying mechanisms of antimicrobial resistance. This figure was created with BioRender.com. MALDI-TOF=matrix-assisted laser desorption/ionisation time-of-flight.

depending on sample type and use of rapid phenotypic methods (figure 2).[73–75] More prolonged testing times can be seen for MDR-GNB, where additional tests for non-first-line antibiotics are often needed. Moreover, in most cases, these phenotypic tests do not provide information regarding the underlying mechanism of resistance, which increasingly helps guide antibiotic therapy and infection prevention and control interventions.

Current rapid diagnostics

There are multiple biochemical assays aimed at rapid identification of AMR in MDR-GNB, with a particular focus on carbapenemase detection.[76,77] These include CarbaNP (an assay developed to detect the presence of carbapenemase production), the related Blue Carba and Beta Carba assays,[78–80] and the carbapenemase inactivation method.[76,81] Similar tests have also been developed for the detection of colistin and cefiderocol resistance.[82,83]

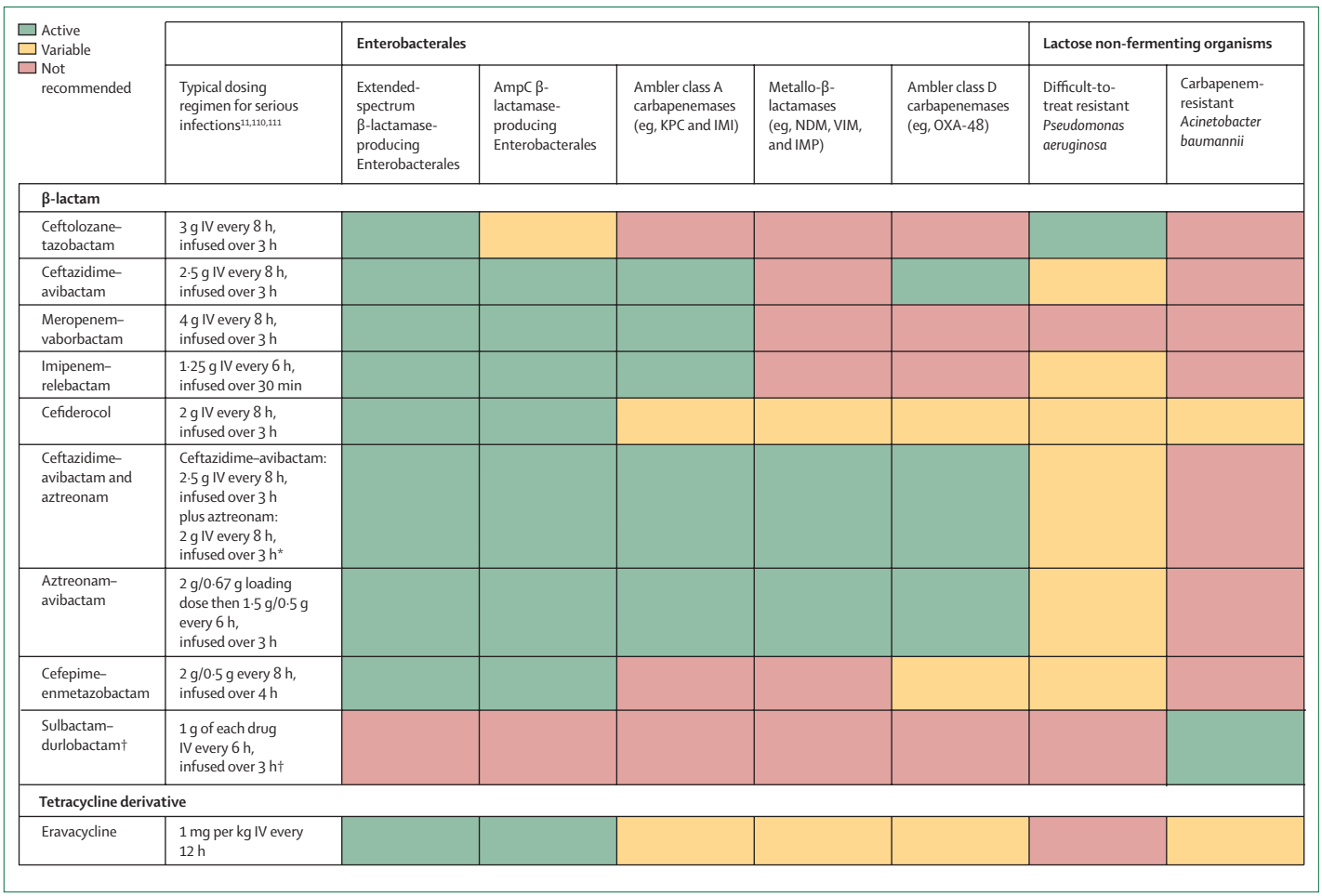
Molecular methods are being extensively used for AMR detection in clinical microbiology laboratories and have high sensitivity and rapid turnaround time (typically the same day to detect a broad category—eg, genes encoding KPCs).[8,76,84,85] PCR-based methods that rely on nucleic acid amplification focus on acquired resistance genes as targets, including ESBL (eg, CTX-M) and carbapenemase genes (eg, KPC and NDM). While purely PCR-based assays are restricted in the number of targets, microarray technology can use hundreds of DNA probes that hybridise to DNA targets, which allows for the inclusion of numerous bacterial identification and resistance gene targets that can directly inform therapy (also known as theranostics). Several commercial multiplexed PCR and microarray panels are currently in use in clinical microbiology laboratories,[77,84] and data on their clinical effects are being reported. A recent prospective multicentre study noted that PCR testing for the bla_{KPC} carbapenemase gene was associated with faster administration of effective antibiotic therapy (median 24 h *vs* 50 h) and decreased 14-day (16% vs 37%) and 30-day (24% vs 47%) mortality in patients with CRE bacteraemia.[67] Several other single-centre studies showed similar findings following the introduction of rapid diagnostics.[86,87] In addition, two systematic reviews focused on the use of rapid diagnostics in bloodstream infections (not MDR-GNB infections specifically) have been performed. The first review found improvement in timeliness of therapy when coupled with antimicrobial stewardship advice, and an association with mortality reduction.[68] The second noted that rapid diagnostics have the potential to improve timeliness of targeted therapy and possibly improve other patient outcomes, but found there was low overall strength of evidence of effectiveness.[69]

Advances in microscopy have also played an important role in improving diagnosis, particularly through use of automated techniques that enable earlier detection of bacterial growth and high-throughput screening.[88,89] Automated microscopy techniques are being integrated with other diagnostic methods (eg, molecular diagnostics and fluorescence-based methods) and can be analysed using artificial intelligence.[73,90,91] Other approaches currently available but not in widespread use include fluorescence in-situ hybridisation, which has been adapted for rapid bacterial identification and detection of specific AMR genes,[77] T2 magnetic resonance-based biosensing for detection of several Gram-negative pathogens and resistance genes directly from blood, and the use of volatile organic compounds to establish antibiotic susceptibility.[92–95]

Emerging technologies

Several emerging technologies for rapid detection of AMR are undergoing development, including microfluidics, biosensor technologies, immune assays, and proteomic and genomic approaches. We will focus on proteomic and genomic assays but refer the reader to a comprehensive review for a more extensive discussion.[77] Matrix-assisted laser desorption/ionisation-time of flight (MALDI-TOF) mass spectrometry is a commercially available proteomic technology that is routinely used in many clinical microbiology laboratories for rapid organism identification.[96] Rapid species identification can guide initial antibiotic choices, especially if a species with considerable rates of AMR is identified. In addition to this primary use, there has also been growing interest in using MALDI-TOF for AMR detection, including carbapenem resistance, but it has not reached widespread clinical use.[97–99]

The use of pathogen genomics for diagnostic purposes has also garnered increasing interest due to rapid decreases in cost and increases in accuracy of the technologies on offer. These efforts have included whole genome sequencing to characterise individual pathogens,[100,101] and metagenomic approaches to detect multiple pathogens and resistance determinants directly from clinical samples.[102,103] Several studies have shown good correlation in MDR-GNB between genotypic and phenotypic antibiotic susceptibility testing in research settings.[104–106] While phenotypic antibiotic susceptibility testing remains the gold standard, it is often time consuming, suffers from low reproducibility, and for some antibiotics (eg, polymyxins) might be difficult to perform outside of a reference laboratory, thus making genomic testing an attractive addition.[107] However, considerable logistical, technical, and regulatory barriers remain, such as access to sequencing instruments and computational resources, the need for bioinformatics expertise to analyse and interpret sequencing data, and the need for more data from diverse pathogens on the relationship between genotype and phenotype. As a result, pathogen genomics to diagnose AMR in clinical settings remains in development but considerable efforts are underway to facilitate access to this technology.[100,108,109]



		Enterobacterales					Lactose non-fermenting organisms	
	Typical dosing regimen for serious infections[11,110,111]	Extended-spectrum β-lactamase-producing Enterobacterales	AmpC β-lactamase-producing Enterobacterales	Ambler class A carbapenemases (eg, KPC and IMI)	Metallo-β-lactamases (eg, NDM, VIM, and IMP)	Ambler class D carbapenemases (eg, OXA-48)	Difficult-to-treat resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*
β-lactam								
Ceftolozane–tazobactam	3 g IV every 8 h, infused over 3 h							
Ceftazidime–avibactam	2·5 g IV every 8 h, infused over 3 h							
Meropenem–vaborbactam	4 g IV every 8 h, infused over 3 h							
Imipenem–relebactam	1·25 g IV every 6 h, infused over 30 min							
Cefiderocol	2 g IV every 8 h, infused over 3 h							
Ceftazidime–avibactam and aztreonam	Ceftazidime–avibactam: 2·5 g IV every 8 h, infused over 3 h plus aztreonam: 2 g IV every 8 h, infused over 3 h*							
Aztreonam–avibactam	2 g/0·67 g loading dose then 1·5 g/0·5 g every 6 h, infused over 3 h							
Cefepime–enmetazobactam	2 g/0·5 g every 8 h, infused over 4 h							
Sulbactam–durlobactam†	1 g of each drug IV every 6 h, infused over 3 h†							
Tetracycline derivative								
Eravacycline	1 mg per kg IV every 12 h							

Figure 3: **Summary of new antibiotic agents for the treatment of multidrug-resistant Gram-negative bacterial infections**
Green=antibiotic is reliably active in vitro and guideline recommended. Yellow=variable activity; antibiotic might be effective if in vitro susceptibility is shown, clinical data might be lacking to support routine use. Red=not recommended, likely absence of in vitro susceptibility. IV=intravenously. *Administered simultaneously via Y-site administration. †Administration was studied in combination with imipenem–cilastatin.

Treatment

In the last decade, several new antibiotics with activity against MDR-GNBs have reached clinical practice (figure 3). Numerous agents remain in development and several non-pharmacological approaches such as phage and microbiome-based therapies are being investigated. With the advent of newer and more targeted therapies, it has become increasingly important to have a framework of therapy for MDR-GNB that takes into account four key factors: (1) the site of infection (eg, urinary tract, lung, or blood), (2) the severity of infection, (3) the bacterial pathogen causing the infection (eg, Enterobacterales, *Pseudomonas*, *Acinetobacter*), and (4) the likely resistance mechanisms involved (eg, ESBL, AmpC, KPC, or NDM). Internationally recognised treatment guidelines now categorise recommendations based on these four factors (figure 4). There is some divergence in recommendations because of differences in MDR-GNB definitions, regional availability of antibiotics, and varied interpretations of the literature due to the lack of comparative effectiveness trials.[112] In addition, guidelines from several other societies are available.[110,111,113–115]

Established antibiotics for MDR-GNB

Until the newly licensed antibiotics became available (figure 3), options for the treatment of MDR-GNB infections were chiefly restricted to older and sometimes more toxic antibiotics. Antibiotics such as trimethoprim–sulfamethoxazole, quinolones, or nitrofurantoin remain useful for treatment of some MDR-GNB infections (eg, UTIs) if in vitro susceptibility is shown (figure 4).

β-lactam agents also continue to be cornerstones of therapy. Carbapenems (eg, meropenem, imipenem, and ertapenem) are broad spectrum β-lactam agents that are recommended for use against serious infections caused by third-generation cephalosporin-resistant Enterobacterales infections, irrespective of the resistance mechanism (figure 4).[10,11,110,113,114] Of note, ertapenem can be hydrolysed by ESBLs, making it necessary to confirm

IDSA	ESCMID	Comments
3GCephR-E		
ESBL-E cystitis: preferred treatments are nitrofurantoin and trimethoprim–sulfamethoxazole. Alternative treatments include ciprofloxacin, levofloxacin, and carbapenems. Single-dose aminoglycoside or oral fosfomycin (for *Escherichia coli* only) **ESBL-E pyelonephritis or complicated UTIs:** trimethoprim–sulfamethoxazole, ciprofloxacin, and levofloxacin are preferred. Ertapenem, meropenem, or imipenem if there is toxicity to trimethoprim and sulfamethoxazole or fluoroquinolones Alternative treatments include aminoglycoside for a full treatment course **All other ESBL-E infections (including serious infections):** meropenem, imipenem, or ertapenem **AmpC infections:** cefepime for organisms at moderate risk of considerable AmpC production (*Enterobacter cloacae* complex, *Klebsiella aerogenes, Citrobacter freundii*) that test susceptible or susceptible dose dependent	**Bloodstream infection and severe infection:** carbapenem (imipenem or meropenem) **Bloodstream infection with no septic shock:** ertapenem can be considered instead of meropenem or imipenem **Low-risk non-severe infection:** piperacillin–tazobactam, amoxicillin–clavulanic acid or quinolones **Complicated UTIs:** aminoglycosides (for short durations) or intravenous fosfomycin	• ESCMID guidelines use only a categorisation of 3GCephR-E and do not make specific recommendations regarding the mechanism of third-generation cephalosporin resistance
CRE		
Cystitis: preferred treatments are nitrofurantoin, trimethoprim–sulfamethoxazole, ciprofloxacin, or levofloxacin. Alternative treatments include a single dose of an aminoglycoside, oral fosfomycin (for *E. coli* only), colistin,ceftazidime–avibactam, meropenem–vaborbactam, imipenem–relebactam, or cefiderocol **Pyelonephritis or complicated UTIs:** preferred treatments are trimethoprim–sulfamethoxazole, ciprofloxacin, levofloxacin, ceftazidime–avibactam, meropenem–vaborbactam, imipenem–relebactam, or cefiderocol. Alternative treatments are aminoglycosides **Ertapenem-resistant, meropenem-susceptible:** Standard-infusion meropenem or imipenem for cystitis. Extended-infusion meropenem or extended-infusion imipenem for other indications **All other infections (including serious infections):** Treatment depends on carbapenemase testing: (1) no carbapenemase production or carbapenemase testing unavailable: ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–relebactam are preferred treatments. However, choice depends on local epidemiology. If previous MBL (metallo-β-lactamase) or suggestive epidemiology, use the recommendations for MBL producers. (2) KPC producers: meropenem–vaborbactam, ceftazidime–avibactam, and imipenem–relebactam. Cefiderocol is an alternative. (3) MBL (eg, NDM, VIM, and IMP) producers: ceftazidime–avibactam and aztreonam combination therapy, or cefiderocol. (4) OXA-48-like producers: ceftazidime–avibactam is preferred and cefiderocol is an alternative.	**Severe infection:** meropenem–vaborbactam or ceftazidime–avibactam if active in vitro **Non-severe infection:** use of an old antibiotic (eg, aminoglycosides or tigecycline), chosen from among the in vitro active agents on an individual basis and according to the source of infection **Complicated UTI:** aminoglycosides over tigecycline. **MBL and/or resistant to other antibiotics:** Cefiderocol. Ceftazidime–avibactam and aztreonam combination therapy is an alternative	• In CRE infection, carbapenemase testing can be crucial to informing optimal treatment decisions and is encouraged by the IDSA • Cefiderocol has in vitro activity against most CRE infections (regardless of carbapenemase presence), but clinical data are currently scarce. ESCMID recommends cefiderocol as a first-line agent for MBL infection • Older agents such as aminoglycosides, polymyxins, and tigecycline are no longer recommended as first-line options. These agents remain alternative agents if in vitro susceptibility is shown and there is non-susceptibility to first-line therapies. These agents are recommended by the ESCMID to be used in combination therapy with more than one drug active in vitro • Tetracycline antibiotics (eg, tigecycline and eravacycline) can be considered as alternative agents for CRE infection outside the blood and urinary tract, regardless of carbapenemase presence • Co-formulated aztreonam–avibactam can be used instead of ceftazidime–avibactam and aztreonam combination therapy, if available
DTR-*P aeruginosa*		
Cystitis: preferred treatments are ceftolozane–tazobactam, ceftazidime–avibactam, imipenem–relebactam, or cefiderocol. Alternative treatments include a single dose of tobramycin or amikacin **Pyelonephritis or complicated UTIs:** ceftolozane–tazobactam, ceftazidime–avibactam, imipenem–relebactam, or cefiderocol. Alternative treatments are once-daily tobramycin or amikaci. **All other infections (including serious infections):** preferred treatments are ceftolozane–tazobactam, ceftazidime–avibactam, and imipenem–relebactam. Alternatively treat with cefiderocol **MBL (eg, NDM, VIM, or IMP) producers:** cefiderocol	**Severe infection:** ceftolozane–tazobactam if active in vitro. Currently insufficient evidence for use of cefiderocol, imipenem–relebactam or ceftazidime–avibactam	
CRAB		
Sulbactam–durlobactam in combination with a carbapenem (ie, imipenem–cilastatin or meropenem). Alternative treatments are high-dose ampicillin–sulbactam in combination with at least one other agent (ie, polymyxin B, minocycline, tigecycline, or cefiderocol), if sulbactam–durlobactam is not available.	**Hospital-acquired pneumonia or ventilator-associated pneumonia with susceptibility to sulbactam:** ampicillin–sulbactam **CRAB resistant to sulbactam:** a polymyxin or high dose tigecycline **Severe and high-risk infections:** combination therapy including two in vitro active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, or sulbactam combinations) **Meropenem with a minimum inhibitory concentration of 8 mg per L or less:** consider carbapenem combination therapy using high dose extended infusion carbapenem dosing	• Durlobactam does not inhibit MBLs and therefore, other treatment options are required if an MBL is present

Figure 4: **Summary of IDSA and ESCMID guidelines for the treatment of multidrug-resistant Gram-negative bacterial infections**
3GCephR-E=third-generation cephalosporin-resistant Enterobacterales. AmpC-E=β-lactamase producing Enterobacterales. CRAB=carbapenem-resistant *Acinetobacter baumannii*. CRE=carbapenem-resistant Enterobacterales. DTR-*P aeruginosa*=difficult-to-treat resistant-*Pseudomonas aeruginosa*. ESBL-E=extended-spectrum β-lactamase-producing Enterobacterales. ESCMID=European Society for Clinical Microbiology and Infectious Diseases. IDSA=Infectious Diseases Society of America. MBL=metallo-β-lactamase. UTI=urinary tract infection.

ertapenem susceptibility before treatment. Meropenem can still be considered for ertapenem-resistant, meropenem-susceptible organisms.[11] The MERINO trial showed that definitive treatment with meropenem for ceftriaxone-resistant *E coli* and *K pneumoniae* resulted in reduced mortality compared with piperacillin–tazobactam.[116] Reanalysis of the original MERINO data using reference antibiotic susceptibility testing methods indicated that this difference is no longer statistically significant.[117] Further studies are underway to validate these findings (eg, the PETERPEN study, NCT03671967). Based on numerous observational studies, there is a potential role for established β-lactam and β-lactamase inhibitors (eg, piperacillin–tazobactam) in non-serious third-generation cephalosporin-resistant Enterobacterales infections,[10] or as a continuation of therapy if clinical improvement is seen.[11]

For Enterobacterales that produce AmpC (eg, *Enterobacter* spp.), cefepime can be considered.[118,119] While the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend against cefepime use for third-generation cephalosporin-resistant Enterobacterales due to a paucity of data,[10] the Infectious Diseases Society of America (IDSA) guidelines state that cefepime use could be appropriate for AmpC-producing Enterobacterales at moderate risk of considerable AmpC production (eg, *E cloacae* complex, *K aerogenes*, and *C freundii*).[11]

Aminoglycosides remain a treatment option for many MDR-GNB and might have a particular role in UTIs. Aminoglycosides are currently recommended as alternative treatments for UTIs due to third-generation cephalosporin-resistant Enterobacterales, CRE, and DTR-*P aeruginosa* (figure 4), when susceptible. These agents carry risks of nephrotoxicity and ototoxicity, restricting long term use. Polymyxins (including colistin and polymyxin B) are cationic compounds that interact with lipopolysaccharides of the outer membrane of Gram-negative bacteria to cause increased permeability and cell death.[31] These agents were previously first-line CRE therapy, but have considerable toxic effects (eg, nephrotoxicity) and have largely been replaced by novel β-lactam and β-lactamase inhibitor combinations, such as ceftazidime–avibactam, which have been associated with a mortality benefit in CRE treatment and fewer toxic events.[120–122] As part of combination regimens, polymyxins remain a treatment option for serious carbapenem-resistant *A baumannii* (CRAB) infections (figure 4) and might have a role in MDR-GNB infections that are not susceptible to any other antibiotic class.

Tetracycline derivatives, such as minocycline and tigecycline, remain a therapeutic option in combination regimens for treatment of CRAB and CRE infections, but are ineffective against *P aeruginosa*.[25,38] After intravenous administration, tigecycline has rapid tissue distribution leading to poor concentrations in the serum and urine so caution is recommended for treating infection at these sites. Tigecycline also has poor lung penetration leading to concerns regarding its use as a treatment for ventilator-associated pneumonia.[38] Tigecycline is more suited to the treatment of intra-abdominal and skin and soft tissue infections. High doses of tigecycline (ie, 200 mg intravenous loading dose then 100 mg daily) are recommended for use in CRAB and CRE infections.[11]

Fosfomycin is available in both oral and intravenous formulations,[32] and is an alternative treatment for uncomplicated UTI caused by ESBL-*E coli* or CRE-*E coli*.[11] Several Gram-negative organisms (including *K pneumoniae*) have intrinsic resistance to fosfomycin due to the presence of *fosA* genes, which might lead to clinical failure.[123,124] In a recent multicentre randomised controlled trial, intravenous fosfomycin did not show non-inferiority to β-lactam therapy for ESBL *E coli* bloodstream infection from a urinary source, however this was due to discontinuation because of side-effects in the fosfomycin group, with clinical cure being similar for both groups.[125]

Sulbactam is an irreversible competitive β-lactamase inhibitor with activity against *A baumannii* (including CRAB) via saturation of penicillin-binding proteins,[63] which is unique to sulbactam and is not shown by other β-lactamase inhibitors. High dose sulbactam in combination with at least one other antibiotic is recommended as a treatment option for CRAB infections (figure 4).[11,126] Of note, sulbactam is typically formulated as ampicillin–sulbactam.

New antibiotics for MDR-GNB

The arrival of multiple newer antibiotics has changed the treatment landscape for MDR-GNB infections. Several new β-lactam and β-lactamase inhibitor combinations have been useful additions for treatment. Ceftolozane–tazobactam pairs a novel fifth-generation cephalosporin with an established β-lactamase inhibitor and has a role in therapy for carbapenem-resistant and DTR-*P aeruginosa* due to ceftolozane's improved affinity for penicillin-binding proteins that render it less affected by porin mutations or efflux pumps.[127] In surveillance studies, 66–98% of all *P aeruginosa* isolates were susceptible to ceftolozane–tazobactam, including 63–95% of MDR *P aeruginosa* isolates.[127–130] As a result, ceftolozane–tazobactam is broadly accepted as first-line therapy for serious DTR-*P aeruginosa* infections if active in vitro. Ceftolozane–tazobactam activity against ESBL-Enterobacterales is mixed, with high rates of susceptibility for ESBL *E coli* (66–100%) but more restricted activity against ESBL *K pneumoniae* (42–84%).[127,130]

Other new combinations include ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–relebactam. These agents are now first-line treatments for CRE infection and their activity varies depending on carbapenemase class. These combinations are active against most organisms producing Ambler class A carbapenemases (eg, KPC), but only ceftazidime–avibactam

has reliable activity against those with Ambler class D carbapenemases such as OXA-48. Observational data suggest that meropenem–vaborbactam might have a lower likelihood of resistance emergence for KPC-producing bacteria.[131] None of these agents alone are active against organisms producing metallo-β-lactamases (Ambler class B carbapenemases—eg, NDM, VIM, and IMP).[132–134] In this scenario, treatment with a combination of ceftazidime–avibactam and aztreonam is recommended by both the ESCMID and IDSA guidelines.

Aztreonam is a monobactam β-lactam with stability against metallo-β-lactamases, while avibactam (given as ceftazidime–avibactam) inhibits the serine β-lactamases that can breakdown aztreonam and are often found concurrently in metallo-β-lactamase-producing organisms. Co-formulated aztreonam–avibactam has been approved for use by the European Medicines Agency (EMA) and is expected for US Food and Drug Administration (FDA) submission. Ceftazidime–avibactam and imipenem–relebactam are also active against MDR-*P aeruginosa*, with susceptibility rates ranging from 68–89% for ceftazidime–avibactam and 59–60% for imipenem–relebactam.[130] There is a difference in recommendations regarding their use for treatment of DTR-*P aeruginosa* with a conditional recommendation from the IDSA, but not the ESCMID. Cefepime–enmetazobactam is a novel combination with activity against ESBL (eg, CTX-M, SHV, and TEM), AmpC, and OXA-48-producing Enterobacterales.[135] This combination was approved for use by the EMA and FDA in 2024, following a phase 3 trial that showed non-inferiority against piperacillin–tazobactam for treatment of complicated UTI and pyelonephritis.[136]

Sulbactam–durlobactam is one of the newest combination agents and was specifically developed to target CRAB infections. Sulbactam has direct activity against *A baumannii* via attachment of penicillin-binding proteins, while durlobactam inhibits Ambler class A, C, and D β-lactamases (including OXA carbapenemases). A phase 3 trial showed non-inferiority to colistin with a statistically significantly lower incidence of nephrotoxicity leading to FDA approval for treatment of hospital-acquired and ventilator-associated pneumonia.[137] Clinical data and availability are restricted, but given the paucity of alternative therapies, sulbactam–durlobactam is an emerging treatment option for CRAB infections and was recommended (in combination with a carbapenem) as first-line therapy by the IDSA. Notably, in the registration trial, sulbactam–durlobactam was used in combination with imipenem–cilastatin but the role of adjunctive carbapenem therapy in clinical use remains to be established.[137,138]

Durlobactam is not active against metallo-β-lactamases (eg, NDM) and alternative regimens should be considered for treatment of metallo-β-lactamase-producing CRAB infections. Due to the high prevalence of CRAB in some countries and the lack of availability of sulbactam–durlobactam, less well-studied combinations that aim to have a similar effect are being explored. Similar to durlobactam, avibactam inhibits Ambler class A, C, and D β-lactamases.[130] Combining avibactam with sulbactam has therefore been suggested as a potential treatment for CRAB, but clinical data are absent.[139,140]

Cefiderocol is a siderophore cephalosporin with a novel mechanism of action. By binding to iron, cefiderocol more easily enters bacterial cells via iron transporters, affording it protection from β-lactamases (including carbapenemases), porin mutations, and efflux pumps.[141] As a result, cefiderocol has broad in vitro activity against most MDR-GNB, with susceptibility rates of 97% for CRE (including all carbapenemases), 97% for carbapenem-resistant *P aeruginosa*, and 95% for CRAB.[142] However, metallo-β-lactamase-producing Enterobacterales and *A baumannii* show high rates of non-susceptibility (24·9% [95% CI 16·6–35·5%] and 40·9% [95% CI 34·5–55·4%], respectively), with NDM-producers being most problematic (38·8% [95% CI 22·6–58·0%] and 44·7% [95% CI 34·5–55·4%], respectively).[143] CREDIBLE-CR, a randomised multicentre phase 3 trial, compared cefiderocol with the best available therapy in patients with carbapenem-resistant Gram-negative infections and noted similar clinical and microbiology efficacy, but a numerically higher number of deaths in the cefiderocol group, driven by patients with *Acinetobacter* spp. infections.[144] For CRAB infections, IDSA guidelines recommend that cefiderocol should be restricted to infections refractory to or where there is intolerance to other antibiotics, while the ESCMID guidelines conditionally recommend against its use. Real-world clinical data are now emerging, with a retrospective observational study of cefiderocol use in Italy showing 30-day mortality of 37% and identifying cefiderocol resistance in 28% of tested isolates.[145]

Beyond β-lactams, new tetracycline derivatives have reached clinical use. Eravacycline has good activity against MDR-GNB and received both FDA and EMA approval. Eravacycline has the same mechanism of action as previous tetracycline agents and has the same rapid tissue distribution as tigecycline, but is less affected by common tetracycline resistance mechanisms such as efflux.[146] Eravacycline has a similar spectrum of activity as tigecycline, including activity against ESBLs, CRE, and CRAB, but not *P aeruginosa*, with minimum inhibitory concentrations being two-fold to four-fold lower against CRE than tigecycline.[147]

Agents in development

Several gaps in our pharmacological armamentarium for treating MDR-GNB exist. Apart from eravacycline, the described new agents require intravenous administration highlighting the need for oral alternatives. Oral carbapenems, such as tebipenem and sulopenem, are highly active against ESBL-producing Enterobacterales (ESBL-E) and have undergone phase 3 trials. In Japan,

tebipenem has been approved for clinical use.[148–151] These agents could have a role for treatment of complicated UTIs and pyelonephritis caused by ESBL-E. Pivmecillinam has extensive activity against ESBL-E with more than 80% isolates being susceptible to treatment.[152] After longstanding use in Europe, pivmecillinam has now been approved for use by the FDA in uncomplicated UTIs. Gepotidacin is a new oral type IIA topoisomerase inhibitor with activity against ESBL-E and fluoroquinolone-resistant isolates.[153] Two phase 3 trials (EAGLE-2 and EAGLE-3) compared gepotidacin with nitrofurantoin for treatment of uncomplicated UTI in women and were terminated early due to meeting the combined primary efficacy endpoint favouring gepotidacin (clinical and microbiological resolution at the test-of-cure visit).[154,155]

Several MDR-GNB pathogens still have few treatment options, including metallo-β-lactamase-producing CRE, DTR-*P aeruginosa*, and CRAB. Cefepime–taniborbactam is a promising novel β-lactam and β-lactamase inhibitor combination with activity against these groups (except IMP carbapenemases).[156] A phase 3 trial showed superiority of cefepime–taniborbactam to meropenem for treatment of complicated UTIs and has led to its submission for FDA approval.[157] Cefepime–zidebactam and meropenem–xeruborbactam have a similar spectrum of in vitro activity and are undergoing evaluation.[158,159]

Non-antibiotic approaches

Although the availability of new antibiotics for MDR-GNB infections is promising, almost all agents discussed belong to pre-existing antibiotic classes. Clinical infections with organisms resistant to these agents have already been described,[6,160,161] highlighting the need to develop alternative or adjunctive non-antibiotic treatments. Phage therapy is an example and consists of administering naturally occurring viruses (bacteriophages or "phages") to kill bacterial pathogens.[17] Phages have high specificity for a pathogen and therefore neither contribute to further emergence of AMR nor affect the surrounding microbiota.[162] Phage therapy might also increase antibiotic susceptibility,[163] leading to interest in its use in conjunction with antibiotics for potential synergistic effects and to prevent the emergence of resistance.[164] Clinical data for MDR-GNB treatment are largely restricted to case reports and case series with therapy tested against the most common MDR-GNB pathogens, including ESBL-E, CRE, MDR *P aeruginosa* infections, and CRAB.[162,165–167] Multiple clinical trials are ongoing (NCT05453578, NCT05498363, and NCT04596319). In addition, phages produce phage-derived peptides (eg, endolysins) that are proteins that target the bacterial cell wall to cause lysis. While this process forms part of phage infection strategies, phage-derived peptides have been generated as recombinant proteins and experimentally evaluated as anti-infective treatments (eg, in *A baumannii* infections).[168,169]

Microbiota-based therapies (eg, faecal microbiota transplantation) are another non-antibiotic therapy being investigated for decolonisation of MDR-GNB before the development of active infection. Most studies have been case series and have focused on ESBL-E and CRE, with decolonisation rates varying substantially.[170–172] A single randomised controlled trial did not show a significant difference in ESBL-E or CRE colonisation when non-absorbable antibiotics were administered with faecal microbiota transplantation, but was terminated early due to poor enrolment and numerous trials are ongoing.[173]

Antivirulence therapies are also a potential alternative to antibiotics as these treatments target virulence factors rather than trying to kill or inhibit the growth of pathogens. This approach might cause less selection pressure compared with antibiotics, thus preventing further emergence of AMR.[174] Some antivirulence strategies include targeting bacterial adhesion and colonisation, preventing biofilm formation, interference with bacterial toxins, inhibition of specialised secretion systems, and regulation of virulence gene expression.[175,176] Although promising, these therapies remain investigational and have not undergone extensive clinical trials in Gram-negative pathogens.

Several therapies that enlist the immune system against MDR-GNB pathogens also form important antibiotic alternatives.[177] Antibody treatments typically target virulence factors and have also been combined with small-molecule therapies (eg, antibiotics) to form antibody–drug conjugates, which simultaneously target the pathogen and engage multiple components of the immune system.[177,178] Vaccines for several common MDR-GNB pathogens are in development, including an extra-intestinal pathogenic *E coli* vaccine in phase 3, an enterotoxigenic *E coli* vaccine in phase 2, and a *K pneumoniae* vaccine in a phase 1 and 2 trial.[179] However, vaccines for other important pathogens (eg, *P aeruginosa* and *A baumannii*) are either in preclinical development or are inactive due to several hurdles such as the need for broad coverage among diverse bacterial strains within a species.[180] Mirroring the recent advances in cancer treatment, immunotherapy that targets host immune response (eg, checkpoint inhibition, cytokine therapies, and cellular therapies) rather than the pathogen itself is also in preclinical development for several MDR-GNB pathogens.[177,181]

Antibiotic adjuvants are compounds that enhance the effectiveness of antibiotics and help overcome bacterial resistance.[182] While β-lactam and β-lactamase inhibitor combinations have been the most prominent examples, several other classes are in development. Efflux pump inhibitors prevent bacteria from expelling antibiotics, thus increasing their intracellular concentration and activity. Membrane permeabilisers assist antibiotics in penetrating bacterial cells, especially the outer membrane of Gram-negative bacteria. Some compounds (eg, NV716)

can act as both efflux pump inhibitors and membrane permeabilisers and also remain in preclinical development.[183]

Knowledge gaps in treatment

The role of combination therapy

Before the availability of novel MDR-GNB antibiotics, combination therapy of multiple agents with in vitro efficacy was recommended for CRE, DTR-*P aeruginosa*, and CRAB infections. Clinical data of the efficacy and safety of newer agents have led to acceptance of use of novel β-lactam and β-lactamase inhibitors as monotherapy for most CRE infections and serious DTR-*P aeruginosa* infections where in vitro activity is shown.[10,11,110,113] However, there is a paucity of data regarding the role of newer agents in treating metallo-β-lactamase-producing CRE and CRAB, either as single agents or in combination therapy. While cefiderocol has activity against these organisms,[184] further data from clinical trials are needed.

Duration of therapy for MDR-GNB infections

There have been multiple efforts to shorten the duration of therapy for treatment of bacterial infection but studies have not specifically focused on MDR-GNB.[185] In studies where there was a considerable proportion of MDR-GNB, shorter courses were non-inferior.[186–189] A retrospective observational study of CRE bacteraemia showed similar odds of recurrent bacteraemia or death within 30 days in patients receiving short courses (7–10 days) as in those receiving long courses of active therapy (14–21 days; odds ratio 1·21 [95% CI 0·55–2·31]).[190] Of the guidelines reviewed, only two made specific recommendations regarding duration of therapy,[110,113] while others made no recommendations or stated that therapy for resistant organisms should not differ to that of susceptible organisms with factors such as clinical response, achievement of source control, and the host's immunological status playing an important role in determining duration of therapy.[10,11] Several clinical trials on the duration of therapy with inclusion of MDR-GNB are ongoing (NCT05124977, NCT05124977, NCT05210387, and NCT03005145). Use of biomarkers (eg, procalcitonin) for personalised therapy duration has also been proposed.[191]

Conclusion

Infections caused by MDR-GNB will continue to be a considerable global health problem. We find ourselves at an exciting crossroads with several new diagnostic and antibiotic treatments becoming available. We must define the role of these newer diagnostics and antibiotics in clinical care, in turn allowing us to move towards a more precision-guided approach to treatment of MDR-GNB infections. Our increased ability to rapidly detect underlying resistance mechanisms offers an important opportunity to guide and maximise the utility of novel antibiotics for MDR-GNB infections, which increasingly target specific mechanisms. Early detection of AMR with improved diagnostics also plays a key role in preventing the spread of MDR-GNB by allowing earlier institution of infection prevention and control measures.

Despite these advances, several key challenges remain in improving outcomes for patients with MDR-GNB infections. Many low-income and middle-income countries lack laboratory infrastructure and many of the new diagnostics discussed in this Review are not commonly used outside of reference laboratories,[192] even in resource-rich settings. Similarly, access to new antibiotics is highly restricted. In many regions, these treatments are simply unavailable, and even in resource-rich settings, ensuring access might require innovations in the economics of antibiotic use.[16] Subscription-based rather than use-based models for restricted antibiotics, as recently introduced in the UK,[193] are one such innovation, but ongoing incentives for obtaining regulatory approval and ensuring availability of new treatments post-approval are also needed.[194]

With these new diagnostics and treatments, we need robust clinical trial data to guide management decisions. Clinical trials in MDR-GNB infections struggle to enrol sufficient numbers of patients, making it difficult to obtain meaningful clinical efficacy data that compare new treatments not only to current best-available therapies, but also in head-to-head trials.[195] Furthermore, defining the optimal duration of therapy and identifying meaningful outcomes to study remains challenging. Several novel clinical trial designs specifically address these shortcomings, including Bayesian adaptive randomisation, Sequential Multiple Assignment Randomized Trial-Comparing Personalized Antibiotic Strategies, Desirability of Outcome Rankings, and the DURATIONS design.[196,197]

Lastly, we need to think beyond antibiotics to avoid the Sisyphean cycle of AMR. While non-antibiotic therapies for MDR-GNB infections hold promise, most are at preclinical stages and require substantial development. Preserving new and established treatments with antimicrobial stewardship is therefore an urgent priority, while infection prevention and control remains a cornerstone of stopping further spread of MDR-GNB. Despite the desperate challenges posed by MDR-GNB infections, we now have many more tools in our armamentarium, giving reason for hope that we can better address this crucially important global health issue.

Contributors

NM and AYP contributed to the conceptualisation, literature review, manuscript drafting, and critical revision of the study. A-CU contributed to the conceptualisation, manuscript drafting, and critical revision.

Declaration of interests

NM received research support from the Joint Programme Initiative on AMR and National Health and Medical Research Council Australia (APP2032022) and the Medical Research Future Fund (FSPGN000048), outside the submitted work, and National Health and Medical Research Council of Australia (Emerging Leader 1 Fellowship APP1176324); and consulting fees from Bridger Consulting. AYP received research funding from Merck Sharp & Dohme for an investigator-initiated research project and from the National Health and Medical Research Council of

Australia (Practitioner Fellowship APP1117940). A-CU received funding from the National Institutes of Health (U54 DK104309). The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

References

1 GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet* 2024; **404:** 1199–226.

2 Thompson T. The staggering death toll of drug-resistant bacteria. *Nature* 2022; published online Jan 31. https://doi.org/10.1038/d41586-022-00228-x (preprint).

3 WHO. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. May 17, 2024. https://iris.who.int/bitstream/handle/10665/376776/9789240093461-eng.pdf?sequence=1 (accessed Aug 23, 2024).

4 WHO. Global action plan on antimicrobial resistance. 2015. https://www.emro.who.int/health-topics/drug-resistance/global-action-plan.html (accessed Aug 23, 2024).

5 Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. *N Engl J Med* 2010; **362:** 1804–13.

6 Giddins MJ, Macesic N, Annavajhala MK, et al. Successive emergence of ceftazidime-avibactam resistance through Distinct Genomic Adaptations in bla(KPC-2)-Harboring Klebsiella pneumoniae Sequence Type 307 Isolates. *Antimicrob Agents Chemother* 2018; **62:** e02101–17.

7 Macesic N, Nelson B, Mcconville TH, et al. Emergence of polymyxin resistance in clinical *Klebsiella pneumoniae* through diverse genetic adaptations: a genomic, retrospective cohort study. *Clin Infect Dis* 2020; **70:** 2084–91.

8 Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in Gram-negative bacteria. *Clin Infect Dis* 2019; **69** (suppl 7)**:** S521–28.

9 Karakonstantis S, Kritsotakis EI, Gikas A. Pandrug-resistant Gram-negative bacteria: a systematic review of current epidemiology, prognosis and treatment options. *J Antimicrob Chemother* 2020; **75:** 271–82.

10 Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect* 2022; **28:** 521–47.

11 Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections. *Clin Infect Dis* 2024; purblished online Aug 7. https://doi.org/10.1093/cid/ciae403 (preprint).

12 Ben-Ami R, Rodríguez-Baño J, Arslan H, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing enterobacteriaceae in nonhospitalized patients. *Clin Infect Dis* 2009; **49:** 682–90.

13 Palacios-Baena ZR, Giannella M, Manissero D, et al. Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review. *Clin Microbiol Infect* 2021; **27:** 228–35.

14 van Loon K, Voor In 't Holt AF, Vos MC. A systematic review and meta-analyses of the clinical epidemiology of carbapenem-resistant Enterobacteriaceae. *Antimicrob Agents Ch* 2018; **62:** e01730–17.

15 Voor In 't Holt AF, Mourik K, Beishuizen B, et al. Acquisition of multidrug-resistant Enterobacterales during international travel: a systematic review of clinical and microbiological characteristics and meta-analyses of risk factors. *Antimicrob Resist Infect Control* 2020; **9:** 71.

16 Butler MS, Gigante V, Sati H, et al. Analysis of the clinical pipeline of treatments for drug-resistant bacterial infections: despite progress, more action Is needed. *Antimicrob Agents Chemother* 2022; **66:** e0199121.

17 Gordillo Altamirano FL, Barr JJ. Phage therapy in the postantibiotic era. *Clin Microbiol Rev* 2019; **32:** e00066–18.

18 Lau WYV, Taylor PK, Brinkman FSL, Lee AHY. Pathogen-associated gene discovery workflows for novel antivirulence therapeutic development. *EBioMedicine* 2023; **88:** 104429.

19 K, Bradford PA. Epidemiology of β-lactamase-producing pathogens. *Clin Microbiol Rev* 2020; **33:** 561–37.

20 Fernández L, Hancock RE. Adaptive and mutational resistance: role of porins and efflux pumps in drug resistance. *Clin Microbiol Rev* 2012; **25:** 661–81.

21 Doi Y, Wachino JI, Arakawa Y. Aminoglycoside resistance: the emergence of acquired 16S ribosomal RNA methyltransferases. *Infect Dis Clin North Am* 2016; **30:** 523–37.

22 Garneau-Tsodikova S, Labby KJ. Mechanisms of resistance to aminoglycoside antibiotics: overview and perspectives. *MedChemComm* 2016; **7:** 11–27.

23 Matamoros BR, Serna C, Wedel E, et al. NpmC, a novel A1408 16S rRNA methyltransferase conferring pan-aminoglycoside resistance discovered in the gut of humans and animals. ESCMID Global 2024; April 27–30, 2024 (abstr).

24 Kawai A, Suzuki M, Tsukamoto K, Minato Y, Doi Y. Functional and structural characterization of acquired 16S rRNA methyltransferase NpmB1 conferring pan-aminoglycoside resistance. *Antimicrob Agents Chemother* 2021; **65:** e0100921.

25 Grossman TH. Tetracycline antibiotics and resistance. *Cold Spring Harb Perspect Med* 2016; **6:** a025387.

26 Lv L, Wan M, Wang C, et al. Emergence of a plasmid-encoded resistance-nodulation-division efflux pump conferring resistance to multiple drugs, including tigecycline, in *Klebsiella pneumoniae*. *MBio* 2020; **11:** e02930–19.

27 Sun J, Chen C, Cui CY, et al. Plasmid-encoded tet(X) genes that confer high-level tigecycline resistance in *Escherichia coli*. *Nat Microbiol* 2019; **4:** 1457–64.

28 He T, Wang R, Liu D, et al. Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans. *Nat Microbiol* 2019; **4:** 1450–56.

29 Hooper DC, Jacoby GA. Mechanisms of drug resistance: quinolone resistance. *Ann N Y Acad Sci* 2015; **1354:** 12–31.

30 Redgrave LS, Sutton SB, Webber MA, Piddock LJ. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. *Trends Microbiol* 2014; **22:** 438–45.

31 Poirel L, Jayol A, Nordmann P. Polymyxins: antibacterial activity, susceptibility testing, and resistance mechanisms encoded by plasmids or chromosomes. *Clin Microbiol Rev* 2017; **30:** 557–96.

32 Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. *Clin Microbiol Rev* 2016; **29:** 321–47.

33 Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. *Nat Rev Microbiol* 2015; **13:** 42–51.

34 Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pan-drug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18:** 268–81.

35 Kadri SS, Adjemian J, Lai YL, et al. Difficult-to-treat resistance in Gram-negative bacteremia at 173 US hospitals: retrospective cohort analysis of prevalence, predictors, and outcome of resistance to all first-line agents. *Clin Infect Dis* 2018; **67:** 1803–14.

36 Avent ML, Rogers BA, Cheng AC, Paterson DL. Current use of aminoglycosides: indications, pharmacokinetics and monitoring for toxicity. *Intern Med J* 2011; **41:** 441–49.

37 Vicari G, Bauer SR, Neuner EA, Lam SW. Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia. *Clin Infect Dis* 2013; **56:** 398–404.

38 Stein GE, Babinchak T. Tigecycline: an update. *Diagn Microbiol Infect Dis* 2013; **75:** 331–36.

39 Centers for Disease Control and Prevention. CRE technical information. 2019. https://www.cdc.gov/hai/organisms/cre/technical-info.html (accessed Aug 23, 2024).

40 Castanheira M, Simner PJ, Bradford PA. Extended-spectrum β-lactamases: an update on their characteristics, epidemiology and detection. *JAC Antimicrob Resist* 2021; **3:** dlab092.

41 Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype. *J Antimicrob Chemother* 2017; **72:** 2145–55.

42 Belley A, Morrissey I, Hawser S, Kothari N, Knechtle P. Third-generation cephalosporin resistance in clinical isolates of Enterobacterales collected between 2016–2018 from USA and Europe: genotypic analysis of β-lactamases and comparative in vitro activity of cefepime/enmetazobactam. *J Glob Antimicrob Resist* 2021; **25:** 93–101.

43 WHO, European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022, 2020 data. Jan 26, 2022. https://www.ecdc.europa.eu/sites/default/files/documents/Joint-WHO-ECDC-AMR-report-2022.pdf (accessed Aug 23, 2024).

44 Mendes RE, Mendoza M, Banga Singh KK, et al. Regional resistance surveillance program results for 12 Asia-Pacific nations (2011). *Antimicrob Agents Chemother* 2013; **57:** 5721–26.

45 Jacoby GA. AmpC beta-lactamases. *Clin Microbiol Rev* 2009; **22:** 161–82.

46 Tamma PD, Doi Y, Bonomo RA, et al. A primer on AmpC β-lactamases: necessary knowledge for an increasingly multidrug-resistant world. *Clin Infect Dis* 2019; **69:** 1446–55.

47 Fung-Tomc JC, Gradelski E, Huczko E, Dougherty TJ, Kessler RE, Bonner DP. Differences in the resistant variants of *Enterobacter cloacae* selected by extended-spectrum cephalosporins. *Antimicrob Agents Chemother* 1996; **40:** 1289–93.

48 Choi SH, Lee JE, Park SJ, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC beta-lactamase: implications for antibiotic use. *Antimicrob Agents Chemother* 2008; **52:** 995–1000.

49 Jacobson KL, Cohen SH, Inciardi JF, et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I beta-lactamase-producing organisms. *Clin Infect Dis* 1995; **21:** 1107–13.

50 Kohlmann R, Bähr T, Gatermann SG. Species-specific mutation rates for ampC derepression in Enterobacterales with chromosomally encoded inducible AmpC β-lactamase. *J Antimicrob Chemother* 2018; **73:** 1530–36.

51 Cai B, Echols R, Magee G, et al. Prevalence of carbapenem-resistant Gram-negative infections in the United States predominated by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Open Forum Infect Dis* 2017; **4:** ofx176.

52 Hsu LY, Apisarnthanarak A, Khan E, Suwantarat N, Ghafur A, Tambyah PA. Carbapenem-resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. *Clin Microbiol Rev* 2017; **30:** 1–22.

53 Grundmann H, Glasner C, Albiger B, et al. Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. *Lancet Infect Dis* 2017; **17:** 153–63.

54 Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant enterobacteriaceae: the impact and evolution of a global menace. *J Infect Dis* 2017; **215** (suppl 1)**:** S28–36.

55 Lane CR, Brett J, Schultz M, et al. Search and contain: impact of an integrated genomic and epidemiological surveillance and response program for control of carbapenemase-producing Enterobacterales. *Clin Infect Dis* 2021; **73:** e3912–20.

56 Canton R, Doi Y, Simner PJ. Treatment of carbapenem-resistant *Pseudomonas aeruginosa* infections: a case for cefiderocol. *Expert Rev Anti Infect Ther* 2022; **20:** 1077–94.

57 Horcajada JP, Montero M, Oliver A, et al. Epidemiology and treatment of multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa* infections. *Clin Microbiol Rev* 2019; **32:** e00031–19.

58 Reyes J, Komarow L, Chen L, et al. Global epidemiology and clinical outcomes of carbapenem-resistant *Pseudomonas aeruginosa* and associated carbapenemases (POP): a prospective cohort study. *Lancet Microbe* 2023; **4:** e159–70.

59 Del Barrio-Tofiño E, Zamorano L, Cortes-Lara S, et al. Spanish nationwide survey on *Pseudomonas aeruginosa* antimicrobial resistance mechanisms and epidemiology. *J Antimicrob Chemother* 2019; **74:** 1825–35.

60 Al-Orphaly M, Hadi HA, Eltayeb FK, et al. Epidemiology of multidrug-resistant *Pseudomonas aeruginosa* in the Middle East and North Africa region. *MSphere* 2021; **6:** e00202–21.

61 Rossolini GM, Bochenska M, Fumagalli L, Dowzicky M. Trends of major antimicrobial resistance phenotypes in enterobacterales and gram-negative non-fermenters from ATLAS and EARS-net surveillance systems: Italian vs European and global data, 2008–2018. *Diagn Microbiol Infect Dis* 2021; **101:** 115512.

62 Hamidian M, Nigro SJ. Emergence, molecular mechanisms and global spread of carbapenem-resistant *Acinetobacter baumannii*. *Microb Genom* 2019; **5:** e000306.

63 Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2015; **59:** 1680–89.

64 Wang M, Ge L, Chen L, et al. Clinical outcomes and bacterial characteristics of carbapenem-resistant *Acinetobacter baumannii* among patients from different global regions. *Clin Infect Dis* 2024; **78:** 248–58.

65 Gales AC, Seifert H, Gur D, Castanheira M, Jones RN, Sader HS. Antimicrobial susceptibility of *Acinetobacter calcoaceticus–Acinetobacter baumannii* complex and *Stenotrophomonas maltophilia* clinical isolates: results from the SENTRY antimicrobial surveillance program (1997–2016). *Open Forum Infect Dis* 2019; **6** (suppl 1)**:** S34–46.

66 Lee YL, Ko WC, Hsueh PR. Geographic patterns of *Acinetobacter baumannii* and carbapenem resistance in the Asia-Pacific region: results from the Antimicrobial Testing Leadership and Surveillance (ATLAS) program, 2012–2019. *Int J Infect Dis* 2023; **127:** 48–55.

67 Satlin MJ, Chen L, Gomez-Simmonds A, et al. Impact of a rapid molecular test for *Klebsiella pneumoniae* carbapenemase and ceftazidime–avibactam use on outcomes after bacteremia caused by carbapenem-resistant Enterobacterales. *Clin Infect Dis* 2022; **75:** 2066–75.

68 Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. *Clin Infect Dis* 2017; **64:** 15–23.

69 Buehler SS, Madison B, Snyder SR, et al. Effectiveness of practices to increase timeliness of providing targeted therapy for inpatients with bloodstream infections: a laboratory medicine best practices systematic review and meta-analysis. *Clin Microbiol Rev* 2016; **29:** 59–103.

70 Bartoletti M, Antonelli A, Bussini L, et al. Clinical consequences of very major errors with semi-automated testing systems for antimicrobial susceptibility of carbapenem-resistant Enterobacterales. *Clin Microbiol Infect* 2022; **28:** 1290e1–e4.

71 Banerjee R, Komarow L, Virk A, et al. Randomized trial evaluating clinical impact of RAPid IDentification and Susceptibility testing for Gram-negative bacteremia: RAPIDS-GN. *Clin Infect Dis* 2021; **73:** e39–46.

72 Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. *Clin Infect Dis* 2009; **49:** 1749–55.

73 Datar R, Orenga S, Pogorelcnik R, Rochas O, Simner PJ, van Belkum A. Recent advances in rapid antimicrobial susceptibility testing. *Clin Chem* 2021; **68:** 91–98.

74 Banerjee R, Humphries R. Rapid antimicrobial susceptibility testing methods for blood cultures and their clinical impact. *Front Med* 2021; **8:** 635831.

75 Tabak YP, Vankeepuram L, Ye G, Jeffers K, Gupta V, Murray PR. Blood culture turnaround time in U.S. acute care hospitals and implications for laboratory process optimization. *J Clin Microbiol* 2018; **56:** e00500–18.

76 Lutgring JD, Limbago BM. The problem of carbapenemase-producing-carbapenem-resistant-Enterobacteriaceae detection. *J Clin Microbiol* 2016; **54:** 529–34.

77 Vasala A, Hytönen VP, Laitinen OH. Modern tools for rapid diagnostics of antimicrobial resistance. *Front Cell Infect Microbiol* 2020; **10:** 308.

78 Bernabeu S, Dortet L, Naas T. Evaluation of the β-CARBA™ test, a colorimetric test for the rapid detection of carbapenemase activity in Gram-negative bacilli. *J Antimicrob Chemother* 2017; **72:** 1646–58.

79 Pires J, Novais A, Peixe L. Blue-carba, an easy biochemical test for detection of diverse carbapenemase producers directly from bacterial cultures. *J Clin Microbiol* 2013; **51:** 4281–83.

80 Tijet N, Boyd D, Patel SN, Mulvey MR, Melano RG. Evaluation of the Carba NP test for rapid detection of carbapenemase-producing Enterobacteriaceae and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2013; **57:** 4578–80.

81 van der Zwaluw K, de Haan A, Pluister GN, Bootsma HJ, de Neeling AJ, Schouls LM. The carbapenem inactivation method (CIM), a simple and low-cost alternative for the Carba NP test to assess phenotypic carbapenemase activity in gram-negative rods. *PLoS One* 2015; **10:** e0123690.

82 Nordmann P, Bouvier M, Poirel L, Sadek M. Rapid cefiderocol NP test for detection of cefiderocol susceptibility/resistance in Enterobacterales. *J Antimicrob Chemother* 2022; **77:** 3456–61.

83 Nordmann P, Jayol A, Poirel L. Rapid Detection of polymyxin resistance in Enterobacteriaceae. *Emerg Infect Dis* 2016; **22:** 1038–43.

84 De Angelis G, Grossi A, Menchinelli G, Boccia S, Sanguinetti M, Posteraro B. Rapid molecular tests for detection of antimicrobial resistance determinants in Gram-negative organisms from positive blood cultures: a systematic review and meta-analysis. *Clin Microbiol Infect* 2020; **26:** 271–80.

85 Rhoads DD, Pournaras S, Leber A, et al. Multicenter evaluation of the BIOFIRE blood culture identification 2 panel for detection of bacteria, yeasts, and antimicrobial resistance genes in positive blood culture samples. *J Clin Microbiol* 2023; **61:** e0189122.

86 Walker T, Dumadag S, Lee CJ, et al. Clinical impact of laboratory implementation of Verigene BC-GN microarray-based assay for detection of Gram-negative bacteria in positive blood cultures. *J Clin Microbiol* 2016; **54:** 1789–96.

87 Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. *J Infect* 2014; **69:** 216–25.

88 Göransson J, Sundqvist M, Ghaderi E, et al. Performance of a system for rapid phenotypic antimicrobial susceptibility testing of Gram-negative bacteria directly from positive blood culture bottles. *J Clin Microbiol* 2023; **61:** e0152522.

89 Esse J, Träger J, Valenza G, Bogdan C, Held J. Rapid phenotypic antimicrobial susceptibility testing of Gram-negative rods directly from positive blood cultures using the novel Q-linea ASTar system. *J Clin Microbiol* 2023; **61:** e0054923.

90 Ullberg M, Özenci V. Identification and antimicrobial susceptibility testing of Gram-positive and Gram-negative bacteria from positive blood cultures using the Accelerate Pheno™ system. *Eur J Clin Microbiol Infect Dis* 2020; **39:** 139–49.

91 Sikorski A, Shamsheyeva A, Gamage D, Oppermann N, Bhalodi AA, Humphries RM. Performance of antipseudomonal β-lactams on the Accelerate PhenoTest BC kit against a collection of *Pseudomonas aeruginosa* isolates. *J Clin Microbiol* 2021; **59:** e01781–20.

92 De Angelis G, Posteraro B, De Carolis E, et al. T2Bacteria magnetic resonance assay for the rapid detection of ESKAPEc pathogens directly in whole blood. *J Antimicrob Chemother* 2018; **73** (suppl 4)**:** iv20–26.

93 Snyder JL, Manning B, Shivers R, et al. Detection of antibiotic resistance genes in clinical samples using T2 magnetic resonance. *Open Forum Infect Dis* 2019; **6** (suppl 2)**:** S301–S.

94 Tibbetts R, George S, Burwell R, et al. Performance of the reveal rapid antibiotic susceptibility testing system on Gram-negative blood cultures at a large urban hospital. *J Clin Microbiol* 2022; **60:** e0009822.

95 Peri AM, O'Callaghan K, Rafiei N, et al. Persistence of detectable pathogens by culture-independent systems (T2 magnetic resonance) in patients with bloodstream infection: prognostic role and possible clinical implications. *Clin Infect Dis* 2024; **78:** 283–91.

96 Singhal N, Kumar M, Kanaujia PK, Virdi JS. MALDI-TOF mass spectrometry: an emerging technology for microbial identification and diagnosis. *Front Microbiol* 2015; **6:** 791.

97 Gato E, Anantharajah A, Arroyo MJ, et al. Multicenter performance evaluation of MALDI-TOF MS for rapid detection of carbapenemase activity in Enterobacterales: the future of networking data analysis with online software. *Front Microbiol* 2022; **12:** 789731.

98 Weis C, Cuénod A, Rieck B, et al. Direct antimicrobial resistance prediction from clinical MALDI-TOF mass spectra using machine learning. *Nat Med* 2022; **28:** 164–74.

99 Nguyen HA, Peleg AY, Song J, et al. Predicting *Pseudomonas aeruginosa* drug resistance using artificial intelligence and clinical MALDI-TOF mass spectra. *mSystems* 2024; **9:** e0078924.

100 Beukers AG, Jenkins F, van Hal SJ. Centralised or localised pathogen whole genome sequencing: lessons learnt from implementation in a clinical diagnostic laboratory. *Front Cell Infect Microbiol* 2021; **11:** 636290.

101 Sherry NL, Horan KA, Ballard SA, et al. An ISO-certified genomics workflow for identification and surveillance of antimicrobial resistance. *Nat Commun* 2023; **14:** 60.

102 de Abreu VAC, Perdigão J, Almeida S. Metagenomic approaches to analyze antimicrobial resistance: an overview. *Front Genet* 2021; **11:** 575592.

103 Serpa PH, Deng X, Abdelghany M, et al. Metagenomic prediction of antimicrobial resistance in critically ill patients with lower respiratory tract infections. *Genome Med* 2022; **14:** 74.

104 Bortolaia V, Kaas RS, Ruppe E, et al. ResFinder 4.0 for predictions of phenotypes from genotypes. *J Antimicrob Chemother* 2020; **75:** 3491–500.

105 Rebelo AR, Bortolaia V, Leekitcharoenphon P, et al. One day in Denmark: comparison of phenotypic and genotypic antimicrobial susceptibility testing in bacterial isolates from clinical settings. *Front Microbiol* 2022; **13:** 804627.

106 Ruppe E, Cherkaoui A, Charretier Y, et al. From genotype to antibiotic susceptibility phenotype in the order Enterobacterales: a clinical perspective. *Clin Microbiol Infect* 2020; **26:** 643e1–e7.

107 Macesic N, Bear Don't Walk OJ 4th, Pe'er I, Tatonetti NP, Peleg AY, Uhlemann AC. Predicting phenotypic polymyxin resistance in *Klebsiella pneumoniae* through machine learning analysis of genomic data. *mSystems* 2020; **5:** e00656–19.

108 Rossen JWA, Friedrich AW, Moran-Gilad J. Practical issues in implementing whole-genome-sequencing in routine diagnostic microbiology. *Clin Microbiol Infect* 2018; **24:** 355–60.

109 Forde BM, Bergh H, Cuddihy T, et al. Clinical implementation of routine whole-genome sequencing for hospital infection control of multi-drug resistant pathogens. *Clin Infect Dis* 2023; **76:** e1277–84.

110 Lawandi A, Yek C, Kadri SS. IDSA guidance and ESCMID guidelines: complementary approaches toward a care standard for MDR Gram-negative infections. *Clin Microbiol Infect* 2022; **28:** 465–69.

111 Al Salman J, Al Dabal L, Bassetti M, et al. Management of infections caused by WHO critical priority Gram-negative pathogens in Arab countries of the Middle East: a consensus paper. *Int J Antimicrob Agents* 2020; **56:** 106104.

112 Hawkey PM, Warren RE, Livermore DM, et al. Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. *J Antimicrob Chemother* 2018; **73** (suppl 3)**:** iii2–78.

113 Pintado V, Ruiz-Garbajosa P, Aguilera-Alonso D, et al. Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria. *Enferm Infecc Microbiol Clin* 2023; **41:** 360–70.

114 Sy CL, Chen P-Y, Cheng C-W, et al. Recommendations and guidelines for the treatment of infections due to multidrug resistant organisms. *J Microbiol Immunol Infect* 2022; **55:** 359–86.

115 Meschiari M, Asquier-Khati A, Tiseo G, et al. Treatment of infections caused by multidrug-resistant Gram-negative bacilli: a practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases. *Int J Antimicrob Agents* 2024; **64:** 107186.

116 Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin–tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. *JAMA* 2018; **320:** 984–94.

117 Henderson A, Paterson DL, Chatfield MD, et al. Association between minimum inhibitory concentration, beta-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study. *Clin Infect Dis* 2021; **73:** e3842–50.

118 Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; thirty-fourth informational supplement. CLSI document M100. 34th ed. CLSI, 2024.

119 European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 14.0, 2024. 2024. https://www.eucast.org/clinical_breakpoints (accessed Aug 23, 2024).

120 Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis* 2020; **70:** 1799–808.

121 Shields RK, Nguyen MH, Chen L, et al. Ceftazidime–avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents Ch* 2017; **61:** e00883–17.

122 van Duin D, Lok JJ, Earley M, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. *Clin Infect Dis* 2018; **66:** 163–71.

123 Abbott IJ, van Gorp E, Wyres KL, et al. Oral fosfomycin activity against *Klebsiella pneumoniae* in a dynamic bladder infection in vitro model. *J Antimicrob Chemother* 2022; **77:** 1324–33.

124 Ito R, Mustapha MM, Tomich AD, et al. Widespread fosfomycin resistance in Gram-negative bacteria attributable to the chromosomal *fosA* gene. *MBio* 2017; **8:** e00749-17.

125 Sojo-Dorado J, López-Hernández I, Rosso-Fernandez C, et al. Effectiveness of fosfomycin for the treatment of multidrug-resistant *Escherichia coli* bacteremic urinary tract infections: a randomized clinical trial. *JAMA Netw Open* 2022; **5:** e2137277.

126 Bartal C, Rolston KVI, Nesher L. Carbapenem-resistant *Acinetobacter baumannii*: colonization, infection and current treatment options. *Infect Dis Ther* 2022; **11:** 683–94.

127 Lizza BD, Betthauser KD, Ritchie DJ, Micek ST, Kollef MH. New perspectives on antimicrobial agents: ceftolozane–tazobactam. *Antimicrob Agents Chemother* 2021; **65:** e0231820.

128 Sader HS, Carvalhaes CG, Duncan LR, Flamm RK, Shortridge D. Susceptibility trends of ceftolozane/tazobactam and comparators when tested against European Gram-negative bacterial surveillance isolates collected during 2012–18. *J Antimicrob Chemother* 2020; **75:** 2907–13.

129 Walkty A, Adam H, Baxter M, et al. In vitro activity of ceftolozane/tazobactam versus antimicrobial non-susceptible *Pseudomonas aeruginosa* clinical isolates including MDR and XDR isolates obtained from across Canada as part of the CANWARD study, 2008–16. *J Antimicrob Chemother* 2018; **73:** 703–08.

130 Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-lactam-β-lactamase inhibitor combinations. *Clin Microbiol Rev* 2020; **34:** e00115–20.

131 Ackley R, Roshdy D, Meredith J, et al. Meropenem–vaborbactam versus ceftazidime–avibactam for treatment of carbapenem-resistant Enterobacteriaceae infections. *Antimicrob Agents Ch* 2020; **64:** e02313–19.

132 Johnston BD, Thuras P, Porter SB, et al. Activity of imipenem–relebactam against carbapenem-resistant *Escherichia coli* isolates from the United States in relation to clonal background, resistance genes, coresistance, and region. *Antimicrob Agents Ch* 2020; **64:** e02408–19.

133 Castanheira M, Doyle TB, Collingsworth TD, Sader HS, Mendes RE. Increasing frequency of OXA-48-producing Enterobacterales worldwide and activity of ceftazidime/avibactam, meropenem/vaborbactam and comparators against these isolates. *J Antimicrob Chemother* 2021; **76:** 3125–34.

134 de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. In vitro susceptibility to ceftazidime–avibactam of carbapenem-nonsusceptible Enterobacteriaceae isolates collected during the INFORM global surveillance study (2012 to 2014). *Antimicrob Agents Ch* 2016; **60:** 3163–69.

135 Morrissey I, Magnet S, Hawser S, Shapiro S, Knechtle P. *In vitro* activity of cefepime–enmetazobactam against Gram-negative isolates collected from U.S. and European hospitals during 2014–2015. *Antimicrob Agents Chemother* 2019; **63:** e00514–19.

136 Kaye KS, Belley A, Barth P, et al. Effect of cefepime/enmetazobactam vs piperacillin/tazobactam on clinical cure and microbiological eradication in patients with complicated urinary tract infection or acute pyelonephritis: a randomized clinical trial. *JAMA* 2022; **328:** 1304–14.

137 Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii*-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). *Lancet Infect Dis* 2023; **23:** 1072–84.

138 Kaye KS, McLeod SM, O'Donnell JP, Altarac D. Sulbactam-durlobactam for infections caused by Acinetobacter baumannii-calcoaceticus complex – Authors' reply. *Lancet Infect Dis* 2023; **23:** e275–76.

139 Dudoignon E, Caméléna F, Lafaurie M, et al. Evolution, control and success of combination therapy with ampicilin–sulbactam/ceftazidime–avibactam during a carbapenem-resistant *Acinetobacter baumannii* outbreak in burn intensive care unit. *Eur J Clin Microbiol Infect Dis* 2024; **43:** 1453–59.

140 Rodriguez CH, Brune A, Nastro M, Vay C, Famiglietti A. *In vitro* synergistic activity of the sulbactam/avibactam combination against extensively drug-resistant *Acinetobacter baumannii*. *J Med Microbiol* 2020; **69:** 928–31.

141 Doi Y. Treatment options for carbapenem-resistant Gram-negative bacterial infections. *Clin Infect Dis* 2019; **69** (suppl 7)**:** S565–75.

142 McCreary EK, Heil EL, Tamma PD. New perspectives on antimicrobial agents: cefiderocol. *Antimicrob Agents Chemother* 2021; **65:** e0217120.

143 Karakonstantis S, Rousaki M, Vassilopoulou L, Kritsotakis EI. Global prevalence of cefiderocol non-susceptibility in Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*: a systematic review and meta-analysis. *Clin Microbiol Infect* 2024; **30:** 178–88.

144 Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* 2021; **21:** 226–40.

145 Piccica M, Spinicci M, Botta A, et al. Cefiderocol use for the treatment of infections by carbapenem-resistant Gram-negative bacteria: an Italian multicentre real-life experience. *J Antimicrob Chemother* 2023; **78:** 2752–61.

146 Alosaimy S, Abdul-Mutakabbir JC, Kebriaei R, Jorgensen SCJ, Rybak MJ. Evaluation of eravacycline: a novel fluorocycline. *Pharmacotherapy* 2020; **40:** 221–38.

147 Morrissey I, Olesky M, Hawser S, et al. *In vitro* activity of eravacycline against Gram-negative bacilli isolated in clinical laboratories worldwide from 2013 to 2017. *Antimicrob Agents Chemother* 2020; **64:** e01699–19.

148 Arends SJR, Rhomberg PR, Cotroneo N, Rubio A, Flamm RK, Mendes RE. Antimicrobial activity evaluation of tebipenem (SPR859), an orally available carbapenem, against a global set of Enterobacteriaceae isolates, including a challenge set of organisms. *Antimicrob Agents Ch* 2019; **63**(6).

149 Cotroneo N, Rubio A, Critchley IA, Pillar C, Pucci MJ. In vitro and in vivo characterization of tebipenem, an oral carbapenem. *Antimicrob Agents Ch* 2020; **64:** e02618–18.

150 Eckburg PB, Muir L, Critchley IA, et al. Oral tebipenem pivoxil hydrobromide in complicated urinary tract infection. *N Engl J Med* 2022; **386:** 1327–38.

151 Sun Z, Su L, Cotroneo N, et al. Evaluation of tebipenem hydrolysis by β-lactamases prevalent in complicated urinary tract infections. *Antimicrob Agents Chemother* 2022; **66:** e0239621.

152 Lodise TP, Kaye KS, Santerre Henriksen A, Kahlmeter G. Review of the in vitro microbiological activity of mecillinam against common uropathogens in uncomplicated urinary tract infection: focus on resistant pathogens. *Open Forum Infect Dis* 2024; **11:** ofae296.

153 Watkins RR, Thapaliya D, Lemonovich TL, Bonomo RA. Gepotidacin: a novel, oral, 'first-in-class' triazaacenaphthylene antibiotic for the treatment of uncomplicated urinary tract infections and urogenital gonorrhoea. *J Antimicrob Chemother* 2023; **78:** 1137–42.

154 Wagenlehner F, Perry CR, Hooton TM, et al. Oral gepotidacin versus nitrofurantoin in patients with uncomplicated urinary tract infection (EAGLE-2 and EAGLE-3): two randomised, controlled, double-blind, double-dummy, phase 3, non-inferiority trials. *Lancet* 2024; **403:** 741–55.

155 Dall C. Trials for novel UTI antibiotic stopped early because of success. 2022. https://www.cidrap.umn.edu/trials-novel-uti-antibiotic-stopped-early-because-success (accessed May 25, 2023).

156 Karlowsky JA, Hackel MA, Wise MG, et al. *In vitro* activity of cefepime–taniborbactam and comparators against clinical isolates of Gram-negative bacilli from 2018 to 2020: results from the Global Evaluation of Antimicrobial Resistance via Surveillance (GEARS) program. *Antimicrob Agents Chemother* 2023; **67:** e0128122.

157 Wagenlehner FM, Gasink LB, McGovern PC, et al. Cefepime–taniborbactam in complicated urinary tract infection. *N Engl J Med* 2024; **390:** 611–22.

158 Mushtaq S, Garello P, Vickers A, Woodford N, Livermore DM. Activity of cefepime/zidebactam (WCK 5222) against 'problem' antibiotic-resistant Gram-negative bacteria sent to a national reference laboratory. *J Antimicrob Chemother* 2021; **76:** 1511–22.

159 Lomovskaya O, Tsivkovski R, Sun D, et al. QPX7728, an ultra-broad-spectrum B-lactamase inhibitor for intravenous and oral therapy: overview of biochemical and microbiological characteristics. *Front Microbiol* 2021; **12:** 697180.

160 Poirel L, Sadek M, Kusaksizoglu A, Nordmann P. Co-resistance to ceftazidime–avibactam and cefiderocol in clinical isolates producing KPC variants. *Eur J Clin Microbiol Infect Dis* 2022; **41:** 677–80.

161 Rubio AM, Kline EG, Jones CE, et al. In vitro susceptibility of multidrug-resistant *Pseudomonas aeruginosa* following treatment-emergent resistance to ceftolozane–tazobactam. *Antimicrob Agents Ch* 2021; **65:** e00084–21.

162 Uyttebroek S, Chen B, Onsea J, et al. Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review. *Lancet Infect Dis* 2022; **22:** e208–20.

163 Gordillo Altamirano F, Forsyth JH, Patwa R, et al. Bacteriophage-resistant *Acinetobacter baumannii* are resensitized to antimicrobials. *Nat Microbiol* 2021; **6:** 157–61.

164 Venturini C, Petrovic Fabijan A, Fajardo Lubian A, Barbirz S, Iredell J. Biological foundations of successful bacteriophage therapy. *EMBO Mol Med* 2022; **14:** e12435.

165 Aslam S, Lampley E, Wooten D, et al. Lessons learned from the first 10 consecutive cases of intravenous bacteriophage therapy to treat multidrug-resistant bacterial infections at a single center in the United States. *Open Forum Infect Dis* 2020; **7:** ofaa389.

166 Kuipers S, Ruth MM, Mientjes M, de Sevaux RGL, van Ingen J. A Dutch case report of successful treatment of chronic relapsing urinary tract infection with bacteriophages in a renal transplant patient. *Antimicrob Agents Ch* 2019; **64:** e01281–19.

167 Wu N, Dai J, Guo M, et al. Pre-optimized phage therapy on secondary *Acinetobacter baumannii* infection in four critical COVID-19 patients. *Emerg Microbes Infect* 2021; **10:** 612–18.

168 Vasina DV, Antonova NP, Grigoriev IV, et al. Discovering the potentials of four phage endolysins to combat Gram-negative infections. *Front Microbiol* 2021; **12:** 748718.

169 Defraine V, Schuermans J, Grymonprez B, et al. Efficacy of artilysin Art-175 against resistant and persistent *Acinetobacter baumannii*. *Antimicrob Agents Chemother* 2016; **60:** 3480–88.

170 Bilsen MP, Lambregts MMC, van Prehn J, Kuijper EJ. Faecal microbiota replacement to eradicate antimicrobial resistant bacteria in the intestinal tract – a systematic review. *Curr Opin Gastroenterol* 2022; **38:** 15–25.

171 Gargiullo L, Del Chierico F, D'Argenio P, Putignani L. Gut microbiota modulation for multidrug-resistant organism decolonization: present and future perspectives. *Front Microbiol* 2019; **10:** 1704.

172 Macareño-Castro J, Solano-Salazar A, Dong LT, Mohiuddin M, Espinoza JL. Fecal microbiota transplantation for carbapenem-resistant Enterobacteriaceae: a systematic review. *J Infect* 2022; **84:** 749–59.

173 Huttner BD, de Lastours V, Wassenberg M, et al. A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant Enterobacteriaceae: a randomized clinical trial. *Clin Microbiol Infect* 2019; **25:** 830–38.

174 Rasko DA, Sperandio V. Anti-virulence strategies to combat bacteria-mediated disease. *Nat Rev Drug Discov* 2010; **9:** 117–28.

175 Dickey SW, Cheung GYC, Otto M. Different drugs for bad bugs: antivirulence strategies in the age of antibiotic resistance. *Nat Rev Drug Discov* 2017; **16:** 457–71.

176 Fleitas Martínez O, Cardoso MH, Ribeiro SM, Franco OL. Recent Advances in anti-virulence therapeutic strategies with a focus on dismantling bacterial membrane microdomains, toxin neutralization, quorum-sensing interference and biofilm inhibition. *Front Cell Infect Microbiol* 2019; **9:** 74.

177 Theuretzbacher U, Outterson K, Engel A, Karlén A. The global preclinical antibacterial pipeline. *Nat Rev Microbiol* 2020; **18:** 275–85.

178 Lovey A, Krel M, Borchardt A, et al. Development of novel immuno-prophylactic agents against multidrug-resistant Gram-negative bacterial infections. *Antimicrob Agents Chemother* 2021; **65:** e0098521.

179 Frost I, Sati H, Garcia-Vello P, et al. The role of bacterial vaccines in the fight against antimicrobial resistance: an analysis of the preclinical and clinical development pipeline. *Lancet Microbe* 2023; **4:** e113–25.

180 López-Siles M, Corral-Lugo A, McConnell MJ. Vaccines for multidrug resistant Gram negative bacteria: lessons from the past for guiding future success. *FEMS Microbiol Rev* 2021; **45:** fuaa054.

181 McCulloch TR, Wells TJ, Souza-Fonseca-Guimaraes F. Towards efficient immunotherapy for bacterial infection. *Trends Microbiol* 2022; **30:** 158–69.

182 Wright GD. Antibiotic adjuvants: rescuing antibiotics from resistance. *Trends Microbiol* 2016; **24:** 862–71.

183 Wang G, Brunel JM, Preusse M, et al. The membrane-active polyaminoisoprenyl compound NV716 re-sensitizes *Pseudomonas aeruginosa* to antibiotics and reduces bacterial virulence. *Commun Biol* 2022; **5:** 871.

184 Timsit J-F, Paul M, Shields RK, et al. Cefiderocol for the treatment of infections due to metallo-B-lactamase-producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 randomized studies. *Clin Infect Dis* 2022; **75:** 1081–84.

185 Haddad SF, Allaw F, Kanj SS. Duration of antibiotic therapy in Gram-negative infections with a particular focus on multidrug-resistant pathogens. *Curr Opin Infect Dis* 2022; **35:** 614–20.

186 Bae M, Jeong Y, Bae S, et al. Short versus prolonged courses of antimicrobial therapy for patients with uncomplicated *Pseudomonas aeruginosa* bloodstream infection: a retrospective study. *J Antimicrob Chemother* 2021; **77:** 223–28.

187 Giannella M, Pascale R, Toschi A, et al. Treatment duration for *Escherichia coli* bloodstream infection and outcomes: retrospective single-centre study. *Clin Microbiol Infect* 2018; **24:** 1077–83.

188 Sousa A, Pérez-Rodríguez MT, Suárez M, et al. Short- versus long-course therapy in gram-negative bacilli bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2019; **38:** 851–57.

189 Yahav D, Franceschini E, Koppel F, et al. Seven versus 14 days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a noninferiority randomized controlled trial. *Clin Infect Dis* 2019; **69:** 1091–98.

190 Soto CL, Hsu AJ, Lee JH, et al. Identifying effective durations of antibiotic therapy for the treatment of carbapenem-resistant Enterobacterales bloodstream infections: a multicenter observational study. *Clin Infect Dis* 2024; **78:** 27–30.

191 Reyes S, Morel MDP, Kostka J, Nicolau DP. Duration of antibiotic therapy for Enterobacterales and *Pseudomonas aeruginosa*: a review of recent evidence. *Curr Opin Infect Dis* 2021; **34:** 693–700.

192 Pokharel S, Raut S, Adhikari B. Tackling antimicrobial resistance in low-income and middle-income countries. *BMJ Glob Health* 2019; **4:** e002104.

193 Mahase E. UK launches subscription style model for antibiotics to encourage new development. *BMJ* 2020; **369:** m2468.

194 Rex JH, Outterson K. Antibacterial R&D at a crossroads: we've pushed as hard as we can…now we need to start pulling! *Clin Infect Dis* 2021; **73:** e4451–53.

195 Shields RK. Progress and new challenges in combatting the threat of antimicrobial resistance: perspective from an infectious diseases pharmacist. *J Infect Dis* 2024; **229**: 303–06.

196 Stewart AG, Harris PNA, Chatfield M, Evans SR, van Duin D, Paterson DL. Modern clinician-initiated clinical trials to determine optimal therapy for multidrug-resistant Gram-negative infections. *Clin Infect Dis* 2020; **71:** 433–39.

197 Quartagno M, Walker AS, Carpenter JR, Phillips PP, Parmar MK. Rethinking non-inferiority: a practical trial design for optimising treatment duration. *Clin Trials* 2018; **15:** 477–88.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.